* الكتاب يوجد به ميد من الاجل





PHARMACOLOGY AND THERAPEUTICS

FOR
VETERINARY MEDICAL STUDENTS

VOLUME I
(GENERAL
& SYSTEMIC
PHARMACOLOGY)

BY

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PREFACE

Our chief objective is to provide students of Veterinary Medicine with a concise but comprehensive source of Pharmacology which is a very rapidly progressing science in both human and animal fields. The book is written in simple English so that it may be understood as easy as possible. It is also supported by figures, tables and illustrations whenever possible to assist students to utilize and remember pharmacological information provided.

The book is presented in two volumes; Volume I which includes General and Systemic Pharmacology; and Volume II which includes Chemotherapy, Toxicology and Clinical Pharmacology. In addition, laboratory notes "Volume III" & "Volume IV" are also available to help students in memorizing, analyzing and reporting data of their experiments along the practical course of Pharmacology.

We hope our simple book gets acceptance by its readers and any suggestions are highly encouraged and will be highly appreciated.

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I. GENERAL PHARMACOLOGY

I.i. - Introduction

- Pharmacodynamics

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INTRODUCTION

Pharmacology is the science that deals with drugs. It includes knowledge about their sources, physical and chemical properties, action and uses, toxic effect as well as their fate in the body.

The drug is defined as any substance which modify the function of living tissues when applied to or given to the living organism; or means any substance used in the treatment or prevention of diseases.

Branches of pharmacology:

1- **Pharmacodynamics:** is the study that deals with the action of the drugs on the tissue function and their mechanism of action.

2- **Pharmacokinetics:** is the study that deals with the different processes happen to a drug in the body after its administration (fate of the drug in the body) including absorption, distribution, biotransformation (metabolism) and excretion of the drugs.

3- **Clinical pharmacology:** in which the appropriate pharmacodymaic, pharmacometric and pharmacokinetic studies are repeated in healthy and diseased domesticated target species.

4- **<u>Therapeutics (Pharmacotherapy, therapeutic uses)</u>:** is the study that deals with clinical uses of drugs in treatment and prevention of diseases. It is either:

   a. **<u>Curative therapeutics:</u>** when drugs are used for treatment of diseases e.g. antibiotics in infections.

   b. **<u>Prophylactic therapeutics:</u>** when used for the prevention of diseases as vaccines to immunize animals against diseases.

5- **<u>Chemotherapy:</u>** is the study that deals with the treatment of infectious diseases caused by bacteria, fungi, protozoa, worms as well as other external parasites.

6- **<u>Toxicology:</u>** is the study that deals with effect of toxic doses of drugs including toxic symptoms, as well as their treatment. Most of the drugs in large doses act as poisons.

7- **<u>Posology:</u>** is the study of medicine dosage, which varies with the species of animal, the intended effect of the drug and individual tolerance or susceptibility.

   A dose → is the quantity of medication to be administered at one time.

   Dosage → refers to determination and regulation of doses.

8- **<u>Metrology:</u>** is the study of weights and measures.

9- **<u>Pharmacognosy:</u>** is the science of identification of drugs; it includes the description of sources of crude drugs, their physical and chemical characters.

10- **Pharmacy:** is the preparation of drugs and their presentation.
Materia medica → is an old term of pharmacology concerned with the sources, description and preparation of drugs.

OFFICIAL BOOKS OF DRUGS

Intonation on drugs can be obtained from one of the officials (Standard) books. An "Official drug" is the drug listed in one of these official books.

Pharmacopoeia: is an official book containing a selected list of the widely used drugs and medicinal preparations with descriptions of their physical properties and tests for identity, purity and potency. Each pharmacopoeia includes a list of drugs added in this particular edition and also a list of deleted drugs might be deleted from the pharmacopoeia because of their toxic effects and / or availability of other more suitable compounds. Majority of nations publish their own pharmacopoeia e.g. British Pharmacopoeia **(B.P),** United States Pharmacopoeia **(U.S.P),** Egyptian Pharmacopoeia **(E.P),** International Pharmacopoeia **(I.P)** is published by the world Health Organization (W.H.O).

National Formulary (NF): is published by the American Pharmaceutical Association. The selection of drugs in the **N.F** is based on therapeutic merit rather than the extend use of a drug. The **N.F** includes many formulae for pharmaceutical preparations like solutions, tinctures, pills, powders, etc.

British Pharmaceutical Codex (B.P.C): is the British counterpart of N.F and is published by Pharmaceutical Society of Great Britain.

British Veterinary Codex (B.V.C): This book contains the medical substances sand preparations used in veterinary practice. It is published by the Pharmaceutical Society of the Royal College of Veterinary Surgeons and the British Veterinary Association.

New and Non-Official Remedies (N.N.R.) It is an annually publication of the American Medical Association including a description of marketed drugs in an acceptable manner and which satisfy the standards.

PHARMACODYNAMICS

__Def__: Is the study that deals with the action and mechanism of action of drugs.

The action or effect → is the manifestation in the body resulting from its administration.

Mechanism of action → is the way by which the drug produces its action on cell function.

Drugs cannot change the function of cell but only increase the activity of a tissue **(stimulation)** or decrease its activity **(inhibition)**

A drug which induces stimulatory reaction to sensory nerves of skin or mucous membranes is referred to as **irritant.**

TYPES OF DRUG ACTION

1- **Therapeutic action** which is the desired medicinal effect of the drug. It is either:

a. **Local effect** which is the effect of the drug before its absorption into blood e.g. the effect of drugs applied on skin or mucous membranes as ointments, eye drops.

b. **General (systemic) effect** which is the effect of the drug after its absorption into blood and circulates to different tissues of the body e.g. the effect of most drugs given by mouth, injection or inhalation.

c. **Reflex or (indirect) effect** which is not due to direct action of the drug on the tissue concerned but due to reflex action from its irritation of sensory nerves of skin or mucous membranes.

2- **Side action** it is the unwanted effect which accompanying the therapeutic effect of a drug e.g. constipation caused by iron preparations during their use in anaemia.

3- **Toxic action** is the dangerous bad effect caused due to administration of a large dose or incidence of allergic, teratogenic or carcinogenic effects.

MECHANISMS OF DRUG ACTION

Drugs may act either by:

1- **Mechanical** when the drug produces its action without interfering with the function of the cell either externally on the skin as the effect of ointment, or internally on the mucous membranes of intestine as the effect of bismuth carbonate, kaolin.

2- **Chemical** which is due to chemical reaction between the drug and body secretion outside the cell e.g. the effect of sodium bicarbonate when used for treating excess acid secretion in stomach (hyperacidity).

3- **Osmosis** when the drug given in hypertonic solution, absorbed water from blood to the intestine to neutralize osmosis as magnesium sulphate in case of constipation (saline purgative).

4- **Replacement** when a drug is given to substitute a laek in a hormone, mineral or vitamin in the body e.g. calcium in rickets, iron in anaemia, Vitamin K in haemorrhages.

5- **Chelation** certain drugs (chelating agents) react with metallic ions inside the cell forming non-ionized inactive compounds e.g. BAL chelates mercury, EDTA chelates calcium.

6- **On metabolic processes** some drugs act by:

a. Preventing destruction of certain endogenous substances by their enzymes e.g. physostigmine prevents destruction of acetylcholine by cholinesterase enzyme.

b. Preventing the cells from utilization of certain substances needed for their growth e.g. sulphonamides prevent bacterial cells to take PABA needed for their growth and multiplication.

7- **On cell division** as cytotoxic effect of anticancer drugs.

8- **On cell receptors**

Receptors ⇒ can be defined as functional macromolecular components or reactive areas of the cell surface with which specific

drugs react forming a complex (**drug / receptor complex**) and causes a response.

***This drug is called (agonist)** e.g. the effect of acetylcholine on cholinergic receptors.

* but if the drug reacts with receptors and causes no effect **the drug is called (antagonist)**

* Antagonists block or prevent the action of agonists on receptors e.g. atropine blocks the action of acetylcholine on cholinergic receptors.

- **Agonist** is defined as the drug which occupying its specific receptors to form agonist-receptor complex, resulting in a response such as secretion of a gland or contraction of a muscle.
- **Complete agonists** are these which induced greatest possible response when they interact with their receptors.
- **Partial agonists** are these which even in large doses can induce a response which is less than the tissue's maximum response.
- **Antagonists** are drugs which have a greater affinity to the receptor, but produce no effect. Antagonists have similar structures as agonists and able to occupy the same specific receptor forming antagonist-receptor complex without any intrinsic activity so prevent the agonist from inducing its activity.

DRUG INTERACTION

This refers to that when two drugs are given together, one of them may influence the potency of the other. The expected effect may be increased or decreased (synergism or antagonism).

Types of interactions:

1- Antagonism between drugs:

It is opposition in action of two drugs when given together.

Types of drug antagonism:

a) **Chemical antagonism** happens when two drugs react chemically to form an inactive complex. e.g. as that happens between acid and alkaline in treating gastric hyperacidity; and using chelating agent containing sulfhydryl group (SH) as dimercaprol (BAL) for inactivation and removal of mercury or arsenic.

b) **Physiological antagonism** the drugs act on two different receptors e.g. adrenaline antagonizes histamine, because adrenaline stimulates the adrenergic receptors causing constriction of cutaneous blood vessels, while histamine causes their dilation by acting on histamine receptors.

c) **Pharmacological antagonism** when the drug prevents the pharmacological action of another drug; this may be competitive or non-competitive.

   i. **Competitive antagonism** when the two drugs compete for the same receptors. This may be **(a) Reversibie** when increasing effect (blocking effect) of the other drug

(antagonist) on the same receptors e.g. when increasing the amount of acetylcholine this can antagonize the blocking effect of atropine on peripheral cholinergic nerves. **(b) Irreversible** when increasing the dose of one drug this doesn't remove the blocking effect of the other drug on the same receptors e.g. adrenergic blockers (as phentolamine) with adrenaline.

ii. **Non-competitive antagonism** when the two drugs act on completely two different sites of action e.g. acetylcholine with papaverine on smooth muscles by acting on cholinergic receptors, while papaverine relaxes them by direct action on their muscles.

Important uses of drug antagonism:

(1) To correct side effects of drugs as the use of mag sulphate to counteract the bad constipating effect of iron sulphate during its use as haematenic in anaemia.

(2) To treat drug toxicity as the use of mephensin or chloral hydrate for treating strychnine poisoning.

2- Enhancement of drug effects

A- Additive drug effects (summation) occur if two drugs with the same effects, when given together produce an effect that is equal in magnitude to the sum of both drugs when given separately e.g. paracetamol and diclofenac as analgesics.

$$1+1 = 2$$

B-Synergism occurs if two drugs with the same effect, when given together, produce an effect that is greater in magnitude than the sum of both drugs when given separately e.g combination between sulpha and trimethoprim

$$1+1=3$$

C- Potentiation occurs if a drug lacking an effect of its own, increases the effect of a second active drug e.g. propencid which delays the excretion of ampicillin.

$$1+0=2$$

ABNORMAL REACTIONS OF THE BODY TO DRUGS

The response of some individuals to the effect of certain drugs may be affected. This may be either tolerance or intolerance.

1- Drug tolerance:

It is the unusual resistance of the body to the effect of normal dose of a drug in certain individuals.

Types of drug tolerance:

Congenital (species or natural) tolerance: certain species of animals can tolerate certain drugs when given in quantities poisonous to other species e.g. rabbits can tolerate atropine as their livers contain large amounts of atropinase enzyme which destroy rapidly atropine.

Acquired tolerance: which develops only on repeated use of certain drugs and after a period, the drug becomes ineffective as by morphine, barbiturates, etc.

Cross tolerance: certain drugs lead to tolerance not only to that drug but also to other related drugs e.g. cross tolerance between alcohols and general anaesthetics. "Addiction" (as by morphine) causes tolerance and withdrawal of morphine leads to mental disturbance because the body becomes adapted to morphine and requires it for its normal function.

2- Drug intolerance

It is the hypersensitivity of the body to the effect of normal dose of a drug in certain individuals.

Types of drug intolerance:

(a) **Hypersensitivity:** when the animal showed symptoms of poisoning after the administration of therapeutic dose of a drug.

(b) **Idiosyncracy:** It is a sensitivity to a drug due to lack of certain enzyme in the body e.g. primaquine may cause haemolytic anaemia in individuals with less glucose-6-phosphate dehydrogenase enzyme.

(c) **Anaphylaxis:** when sudden symptoms of sensitivity happen immediately after drug administration and may cause death. This occurs due to massive release of histamine (after administration of a drug) which causes circulatory collapse and death.

(d) **Allergy:** occurs when symptoms of sensitivity happens slowly (not immediately). Allergy develops within hours to days and

dose not lead to death. It results due to the slow release of histamine. Certain drugs as suphonamides, penicillin, aspirin, liver extract may cause allergy in some individuals. Symptoms of allergy include skin rashes, asthma, fever, low blood pressure, etc.

I.ii. PHARMACOKINETICS

- Pharmacokinetic technique
- Principles of Pharmacotherapeutics
- Drug residues

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PHARMACOKINETIC TECHNIQUE

Aim of pharmacokinetic study to help the understanding of (1) how a drug is handled by the body; (2) how individual variation in response to a fixed dose can be so great, (3) how species variation may be explained, (4) how disease may alter response, and has provided a basis from which dose size and dose frequency recommendations can be made.

It is possible to identify a plasma concentration at which drug effect becomes apparent, to correlate intensity of effect with plasma concentration to equate the duration of effect with the period over which plasma concentration exceeds the threshold value (Fig. 1). The first simplification of the phamacokineticist, i.e. measurement of plasma drug concentration instead of amount and duration of response, is therefore, justifiable.

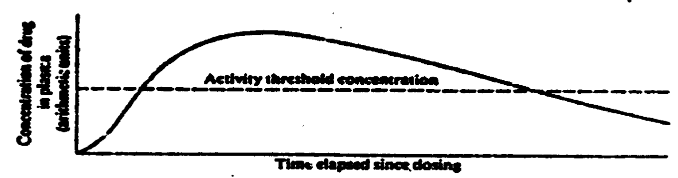


Fig. 1 A hypothetical plasma drug concentration/time curve.

DISPOSITION KINETICS

The process of absorption is the factor which causes plasma drug concentration to rise initially. Distribution, metabolism and excretion will remove free drug from plasma and cause its concentration to fall. These previous processes called disposition, the disposition kinetics of a drug is defined by finding the equation which fits plasma concentration-time curve. The model is used to describe the way in which the body has behaved with regard to the drug in equation.

1) The one -compartment open model:

It is the simplest model in which the body is seen as one continuous fluid phase into which drug is administered and through which the drug instantaneously diffuse to equilibrium. The term open means the continuous loss of drug from the compartment.

Zero-order kinetics are said to be operating and the plasma drug concentration versus time is a straight line. Such a situation is not common but is seen when the elimination process has become saturated i.e. incapable of further increase in elimination e.g. in renal failure or when elimination is dependent on active transport system.

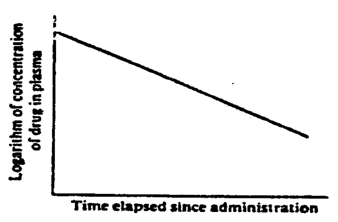


Fig. 2: Idealized graph of plasma concentration plotted against time for a drug for which the body has behaved as a one-compartment open system.

The decline in plasma drug concentration follows first-order kinetics, in which a constant fraction of the presented drug is eliminated in unit time. This relation is straight line if plotted semi-logarithmically (Fig. 2). Such process can be defined by its rate constant which expresses the fractional change per unit time, or by its half-time ($t_{1/2}$).

1) The multi-compartment open model:

More frequently, disposition studies with intravenously injected drugs yield data which even when plotted semi-logarithmically fall on an inflected line (Fig. 3).

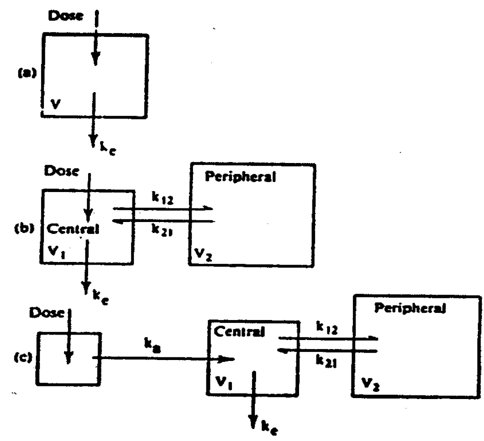


Fig. 3: One comparnment and two-compartment models, represented at (a) and (b). The third compartment in (c) is required for non-intravenous administration. K_e is the rate constant of elimination from the central compartment, while K_{12} and K_{21} are the rate constants of distribution between the central and peripheral compartments. The rate constant of absorption is K_a. V represents in each case the volume of a compartment.

The initial steep fall in plasma drug concentration represents the dominance of the rapid loss of drug due to distribution. The elbow

represents the point at which distribution equilibrium has been achieved and after which the rate of fall decreases and reflects, principally, the continuing loss of drug by elimination alone. In this case, the body behaves as if it were a two compartment open system (Fig 4).

The central compartment allows rapid, more or less instantaneous equilibrium while the peripheral compartment comes to equilibrium with the central one more slowly. The central compartment may be regarded as representing blood, interstitial fluid and highly perfused organs such as heart, lung, liver and kidneys. The peripheral compartment corresponds to the less well perfused organs and tissues as skin, bone and fat.

It is sometimes found that even with intravenous administration, the concentration-time data is best fitted by a tri-exponential expression, in which case a third compartment is invoked

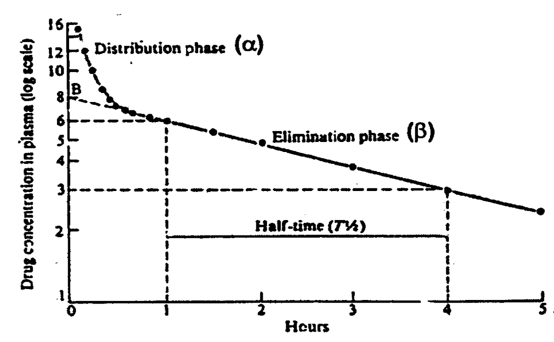


Fig. 4: Idealized plot of plasma concentration at various time intervals after intravenous injection of a drug whose behaviour fits a two-compartment model.

The rate of elimination

A plottypical of two-compartmental behavior is shown in Fig (4). The simple graphical extraction of the drug's half-time ($t_{1/2}$) is displayed. This can be transformed into a value for the apparent overall rate constant of elimination (β) by the following equation:

$$\beta = \frac{0.693}{t_{1/2}}$$

PRINCIPLES OF PHARMACOTHERAPEUTICS

PLASMA DRUG LEVELS

Latency and intensity:

The time taken to achieve that concentration will depend on just two factors; dose and the rate constant of the absorption process. The rate constant defines the fraction of the amount of drug at the site of administration which is absorbed per unit time. Absorption by diffusion follows first order kinetics, which means that the maximum rate of drug absorption occurs shortly after administration. As the residue at the administration site diminishes, so the amount absorbed per unit time is progressively less. The likely overall patterns of plasma drug concentrations following the administration of the same dose by intravenous, intramuscular or subcutaneous injection are illustrated in fig. (5).

Each curve displays the effect of the route of administration on the length of the latent period, the maximum attainable concentration

and the duration of action. The latent period is the time interval between completion of administration and the point at which drug concentration at the site of action is high enough for the drug to be able to exert its characteristic effect. Latency is minimized by using the intravenous route, which is therefore the route of choice when immediate onset of full effect is required, e.g. in treatment of an acute infection.

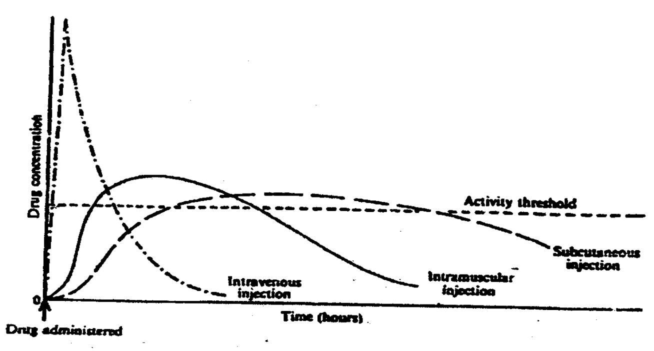


Fig. 5: There is interdependence between (a) the route of administration of a standard dose of a drug, (b) the latent period, (c) the maximum attainable concentration, and (d) the duration of action. The latent period is the interval between drug administration and the crossing of the activity threshold. The period of drug action ends when concentration falls below the threshold.

The intensity of a drug-induced effect has been shown to correlate well with the concentration of the drug in the plasma at the time. The figure plain that the intravenous route is well-suited for inducing a short-acting high-intensity response. Equally it suggests that to achieve a longer-lasting effect of the same intensity a larger dose would have to be given by the other routes of injection. Whether this

would be successful would depend on the maximal rate of absorption from the injection sites.

Duration of action:

Following intravenous injection, the whole dose is immediately present in the central compartment and is therefore exposed to the first-order rate processes of elimination. The higher the concentration presented to such processes, the greater is the amount eliminated per unit time: hence concentration falls exponentially and rapidly.

The longer duration achieved by the other injection routes and the comparatively lower maximum concentrations achieved reflect the length of time taken to complete absorption. For both subcutaneous and intramuscular routes, peak plasma concentration coincides with that period over which the rate of delivery of drug to the central compartment exactly matches the rate of removal by drug disposition processes. The duration of drug effect will be determined by the time taken to bring plasma concentration back down to the activity threshold value. This, in turn, is determined by the volume of distribution of the drug (the greater the volume the longer the elimination time) and the relative contributions of biotransformation and excretion to the elimination process (Fig. 6).

Table 1: Summary

	I.V.	I.M.	S.C.
Latency	Short	Longer	The longest
Intensity	High	Lower	Very low
Duration of action	Short	Longer	Longest

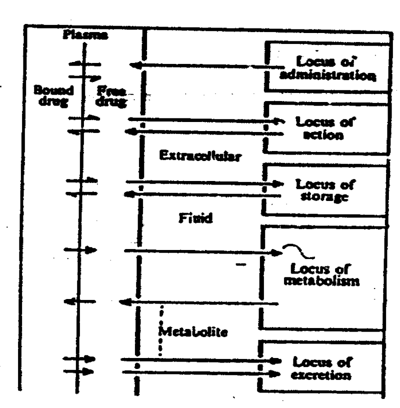


Fig.6: The plasma free-drug concentration is always the product of a dynamic equilibrium. The drug movements which tend to modify this state are represented in this figure by arrows.

MULTIPLE DRUG THRAPY

The use of a mixture of drugs is liable to introduce further variables into dosage computation because of the possibility of a variety of interactions between the components and the patient. The use of a number of drugs is justified only if this achieves greater efficacy or safety; the use of 'shot-gun' therapy or polypharmacy is a poor substitute for skilful and accurate diagnosis. The following sections deal with some of the hazards and concepts peculiar to multiple drug therapy.

1) Increased response

In order to reduce the incidence of drug toxicity, two or more drugs which can elicit the same type of response may be administered together. The final response may be quantitatively equal to the sum of the expected responses had the drugs been used singly: this is termed summation. Summation is exemplified by the use of streptomycin and dihydrostreptomycin mixtures and implies that the component drugs share the same mode of action. Should the actual response be greater than is explainable on the basis of simple summation, then potentiation or synergism is said to have occurred, synergism is exemplified by the use of penicillin and streptomycin mixtures. Explanation for potentiation of action is that two drugs may act sequentially to produce the same effect; e.g pyrimethamine and a sulphonamide sequentially inhibit the synthesis of nucleic acids in coccidia. Advances in the successful management of neoplasia in man have depended very much on comparative studies of the value of drugs given in a variety of combinations and sequences.

2) Decreased response

In multiple drug therapy it sometimes happens that the response seen is less than the sum of the component responses, in which case there has been antagonism between the drugs used. Antagonism can sometimes be explained on the basis of one drug's interfering with or even reversing the action of the other, i.e. it is often dependent on a mechanism involving pharmacological or physiological incompatibility. The use of a mixture which contains a bacteriostatic sulphonamide and a bactericidal antibiotic exemplifies this possibility in that penicillin achieves its greatest antibacterial effect when the organism is multiplying rapidly. A sulphonamide arrests cell division and so reduces the usefulness of the antibiotic.

3) Incompatibility:

This is basically a pharmaceutical problem but can be included conveniently at this point. The components of a mixture may be physically incompatible (e.g. oils and water), or chemically incompatible, when they react together, e.g. acids and alkalis or oxidizing and reducing agents. Of greater importance is the question of physiological or pharmacological incompatibility of drugs given sequentially.

4) Increased toxicity:

Increased toxicity can arise on several counts. Two drugs both of them use the same degradation pathway may compete if the route has a limited capacity. This results in lower-than-useful rates of inactivation of one or both drugs, depending on their relative affinities.

If either has a narrow safety margin; toxicity may occur. An animal which has been exposed to microsomal enzyme inducers may produce reactive intermediates in excess of conjugating capacity and this too may result in enhanced toxicity. Competition for binding sites is another mechanism which can increase the hazard from drugs which are normally highly protein-bound, e.g. coumarin derivative anticoagulants. Drugs whose plasma half-life is markedly shorter than their biological half-life so-called 'hit- and-run' drugs cause increased response to other particular drugs, e.g. organophosphates increase the response to cholinomimetics by diminishing the animal's cholinesterase reserve. Pharmacological incompatibility is exemplified by the use of adrenaline as cardiac stimulant in an animal anaesthetized with a drug which sensitizes the heart to the action of adrenaline e.g. cyclopropane.

5) Decreased toxicity:

A more common example of decreased toxicity is the use of a premedicant tranquilizer before the induction of anaesthesia. This simplifies the process of induction and reduces the dose of barbiturate necessary, a valuable gain in the poor-risk subject. When sulphonamides are being used, the possibility of sulphonamides metabolites coming out of solution in the kidney tubules is much reduced by using sulphonamide mixtures rather than just one of the components at an equivalent dosage.

FACTORS WHICH DETERMINE DOSE FREQUENCY

It is more commonly necessary to extend the duration of action by administering the drug repeatedly.

1) Drug clearance:

The shorter the half-life, the more efficiently a drug is cleared from the body and the shorter will be the interval between doses when a continuing level of effect is required. However, repeat doses are not always of the same size, e.g. an initial loading dose followed by smaller daily maintenance doses is a regimen commonly used in therapy with sulphonamides, and is illustrated in Fig. (7 a). With this method, the first dose is aimed at fulfilling therapeutic requirements, including satisfying sites of loss, while the subsequent doses merely replace that proportion of the loading dose which is lost through metabolism and excretion. In this way, the plasma concentration is maintained at a level compatible with a continuous bacteriostatic effect. When clearance is also aided by the storage of drug in the body, including binding to plasma proteins, then eventual saturation of the storage sites will lead to a rapid increase in blood concentration unless dose size or frequency is carefully adjusted. If, in addition; either the degradation or the excretion of the drug is slow, the situation becomes even more critical. Binding to plasma protein would of itself depress the rates of inactivation and excretion. If these factors operate in such a way that one dose of a drug is not eliminated before the next is administered, then the concentration of drug in the body will increase with each successive dose. This process is known as cumulation and is represented schematically in Fig (7 b). The significance of cumulation

in that the concentration of the drug may rise to toxic levels. Cumulative toxicity is a particular problem with compounds which have a long half-life, e.g. thyroxine, digitalis glycosides, lead, copper and the organochlorine pesticides.

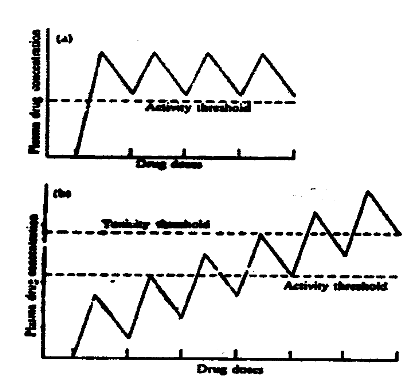


Fig. 7: (a) Probable plasma drug levels obtained by the administration of an initial loading dose, which achieves the desired plasma concentration, followed by smaller maintenance doses which maintain this concentration.
(b) When the increase in plasma drug concentration caused by one dose of a drug is not reversed before the next dose is given, the concentration can increase with each successive dose. This may produce cumulative toxicity.

2) Stability of concentration:

The action of the sulphonamides, for example, depends on their being present at their site of action not only for an adequate period but also at an adequate concentration throughout that period. In general, greater stability is achieved when the total daily dose is given as several divided doses throughout the 24 hr. rather than as a single daily

dose. However, the onset of action is slower when divided doses are used, as a longer interval elapses before a suitable drug concentration is achieved at the site of action. This delay may be avoided by increasing the size of the first dose.

Pharmacokinetics seeks to define the qualitative, quantitative and temporal aspects of:-

1- Absorption of the drug from its site of administration.
2- The manner in which it becomes distributed about the body.
3- The way in which it becomes inactive i.e. biotransformation.
4- The way in which it is eliminated from the body.

1- ABSORPTION OF DRUGS

Absorption is the transfer of a drug from its site of administration to the blood stream. The rate and efficiency of absorption depend on the route of administration. For IV delivery, absorption is complete; that is, the total dose of drug reaches the systemic circulation. Drug delivery by other routes may result in only partial absorption and, thus, lower bioavailability. For example, the oral route requires that a drug dissolve in the GI fluid and then penetrate the epithelial cells of the intestinal mucosa; disease states or the presence of food may affect this process.

A. Transport of a drug from the GI tract:

Depending on their chemical properties, drugs may be absorbed from the GI tract by passive diffusion, active transport, facilitated diffusion and phagocytosis.

1- **Passive diffusion.** The diving force for passive absorption of a drug is the concentration gradient across a membrane separating two body compartments; that is, the drug moves from a region of high concentration to one of lower concentration. Passive diffusion does not involve a carrier. The majority of drugs gain access to the body by this mechanism. Lipid-soluble drugs readily move across most biological membranes, whereas water-soluble drugs penetrate the cell membrane through aqueous channels. (Fig. 8).

2- **Active transport:** This mode of drug entry involves specific carrier proteins that span the membrane. A few drugs that closely resemble the structure of naturally occurring metabolites are actively transported across cell membranes using these specific carrier proteins. Active transport is energy-dependent and is driven by the hydrolysis of adenosine triphosphate (see Fig. 8). It is capable of moving drugs against a concentration gradient—that is, from a region of low drug concentration to one of higher drug concentration.

3- **Facilitated diffusion:** Non lipid soluble drugs can diffuse through the lipid matrix by the help of a carrier system of enzymes from the extracellular to the intracellular fluid along the concentration gradient.

4- Phagocytosis & pinocytosis: Phagocytosis (cell eating) is a process in which most or the entire cell surrounds the molecule. Pinocytosis (cell drinking) involves a small invagination forming in the cell membrane that surrounds the drug molecule and brings it into the cell. Both processes require cellular energy but they are rare methods by which drugs move across membranes.

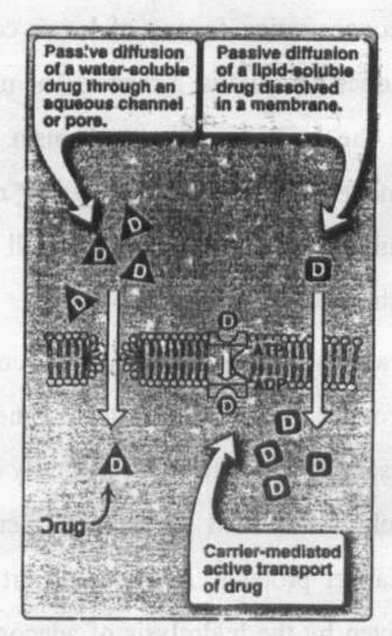


Fig. 8: Schematic representation of drugs crossing a cell membrane of an epithelial cell of the gastrointestinal tract.

B. Physical factors influencing absorption

1. Blood flow to the absorption site: Blood flow to the intestine is much greater than the flow to the stomach; thus, absorption from the intestine is favored over that from the stomach.

2. Total surface area available for absorption: Because the intestine has a surface rich in microvilli, it has a surface area about 1,000-fold that of the stomach; thus, absorption of the drug across the intestine is more efficient.

3. Contact time at the absorption surface: If a drug moves through the GI tract very quickly, as in severe diarrhea, it is not well absorbed. Conversely, anything that delays the transport of the drug from the stomach to the intestine delays the rate of absorption of the drug. Also, the presence of food in the stomach both dilutes the drug and slows gastric emptying. Therefore, a drug taken with a meal is generally absorbed more slowly.

BIOAVAILABILITY

Bioavailability is the fraction of administered drug that reaches the systemic circulation. Bioavailability is expressed as the fraction of administered drug that gains access to the systemic circulation in a chemically unchanged form.

A. Determination of bioavailability

Bioavailability is determined by comparing plasma levels of a drug after a particular route of administration (for example, oral administration), with plasma drug levels achieved by IV injection, in which all of the agent enters the circulation. When the drug is given orally, only part of the administered dose appears in the plasma By plotting plasma concentrations of the drug versus time, one can measure the area under the curve (AUC). Bioavailability of a drug

administered orally is the ratio of the area calculated for oral administration compared with the area calculated for IV injection (Fig. 9).

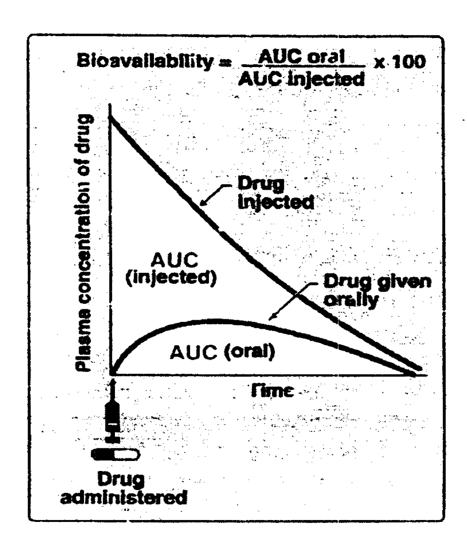


Fig. 9: Determination of the bioavailability of a drug. (AUC = area under curve)

B. Factors that influence bioavailability

1. First-pass hepatic metabolism: When a drug is absorbed across the GI tract, it enters the portal circulation before entering the systemic circulation. If the drug is rapidly metabolized by the liver, the amount of unchanged drug that gains access to the systemic circulation is

decreased. Many drugs, such as propranolol undergo significant biotransformation during a single passage through the liver.

2. Solubility of the drug: Very hydrophilic drugs are poorly absorbed because of their inability to cross the lipid-rich cell membranes. Paradoxically, drugs that are extremely hydrophobic are also poorly absorbed, because they are totally insoluble in the aqueous body fluids and, therefore, cannot gain access to the surface of cells. For a drug to be readily absorbed, it must be largely hydrophobic yet have some solubility in aqueous solutions.

3. Chemical instability: Some drugs, such as penicillin G, are unstable in the pH of the gastric contents. Others, such as insulin, are destroyed in the GI tract by degradative enzymes.

4. Nature of the drug formulation: Drug absorption may be altered by factors unrelated to the chemistry of the drug. For example, particle size, salt form, crystal polymorphism, and the presence of excipients (such as binders and dispersing agents) can influence the ease of dissolution and, therefore, alter the rate of absorption.

2. DRUG DISTRIBUTION

Drug distribution is the process by which a drug reversibly leaves the bloodstream and enters the interstitium (extracellular fluid) and/or the cells of the tissues. The delivery of a drug from the plasma to the interstitium primarily depends on blood flow, capillary permeability, the degree of binding of the drug to plasma and tissue proteins, and the relative hydrophobicity of the drug.

A. Blood flow

The rate of blood flow to the tissue capillaries varies widely as a result of the unequal distribution of cardiac output to the various organs. Blood flow to the brain, liver, and kidney is greater than that to the skeletal muscles, and adipose tissue has a still lower rate of blood flow. This differential blood flow partly explains the short duration of hypnosis produced by a bolus intravenous injection of thiopental. The high blood flow together with the superior lipid solubility of thiopental permit it to rapidly move into the central nervous system (CNS) and produce anesthesia. Slower distribution to skeletal muscle and adipose tissue lowers the plasma concentration sufficiently so that the higher concentrations within the CNS decrease and consciousness is regained. Although this phenomenon occurs with all drugs to some extent, redistribution accounts for the extremely short duration of action of thiopental and compounds of similar chemical and pharmacologic properties.

B. Capillary permeability

Capillary permeability is determined by capillary structure and by the chemical nature of the drug.

1. Capillary structure: Capillary structure varies widely in terms of the fraction of the basement membrane that is exposed by slit junctions between endothelial cells. In the brain, the capillary structure is continuous, and there are no slit junctions. This contrasts with the liver and spleen, where a large part of the basement membrane is exposed due to large, discontinuous capillaries through which large plasma proteins can pass.

Blood-brain barrier: To enter the brain, drugs must pass through the endothelial cells of the capillaries of the CNS or be actively transported. For example, the large, neutral amino acid carrier transports levodopa into the brain. Lipid-soluble drugs readily penetrate into the CNS, because they can dissolve in the membrane of the endothelial cells. Ionized or polar drugs generally fail to enter the CNS, because they are unable to pass through the endothelial cells of the CNS, which have no slit junctions. These tightly juxtaposed cells form tight junctions that constitute the so-called blood-brain barrier.

2. Drug structure: The chemical nature of the drug strongly influences its ability to cross cell membranes. Hydrophobic drugs, which have a uniform distribution of electrons and no net charge, readily move across most biological membranes. These drugs can dissolve in the lipid membranes and, therefore, permeate the entire cell's surface. The major factor influencing the hydrophobic drug's distribution is the blood flow to the area. By contrast, hydrophilic drugs, which have either a nonuniform distribution of electrons or a positive or negative charge, do not readily penetrate cell membranes and must go through the slit junctions.

C. Binding of drugs to proteins

Plasma albumin is the major drug-binding protein, and may act as a drug reservoir; that is, as the concentration of the free drug decreases due to elimination by metabolism or excretion, the bound drug dissociates from the protein. This maintains the free-drug concentration as a constant fraction of the total drug in the plasma. Bound drugs are pharmacologically inactive; only the free, unbound

drug can act on target sites in tissues, elicit a biologic response, and be available to the processes of elimination.

A. Binding capacity of albumin

The binding of drugs to albumin is reversible, and may show low capacity (one drug molecule per albumin molecule) or high capacity (a number of drug molecules binding to a single albumin molecule). Drugs can also bind with varying affinities. Albumin has the strongest affinity for anionic drugs (weak acids) and hydrophobic drugs. Most hydrophilic drugs and neutral drugs do not bind to albumin. Many drugs are hydrophobic by design, because this property permits absorption after oral administration.

B. Competition for binding between drugs

When two drugs are given, each with high affinity for albumin, they compete for the available binding sites. The drugs with high affinity for albumin can be divided into two classes, depending on whether the dose of drug (the amount of drug found in the body under conditions used clinically) is greater than or less than the binding capacity of albumin (quantified as the number of millimoles of albumin multiplied by the number of binding sites) (Fig. 10).

1- **Class I drugs:** If the dose of drug is less than the binding capacity of albumin, then the dose/capacity ratio is low. The binding sites are in excess of the available drug, and the bound-drug fraction is high. This is the case for Class I drugs, which includes the majority of clinically useful agents.

2- **Class II drugs:** These drugs are given in doses that greatly exceed the number of albumin binding sites. The dose/capacity ratio is high, and a relatively high proportion of the drug exists in the free state, not bound to albumin.

3- **Clinical importance of drug displacement:** This assignment of drug classification assumes importance when a patient who is taking a Class I drug, such as tolbutamide, is given a Class II drug, such as a sulfonamide antibiotic. Tolbutamide is normally 95 percent bound, and only five percent is free. This means that most of the drug is sequestered on albumin, and is inert in terms of exerting pharmacologic actions. If a sulfonamide is administered, it displaces

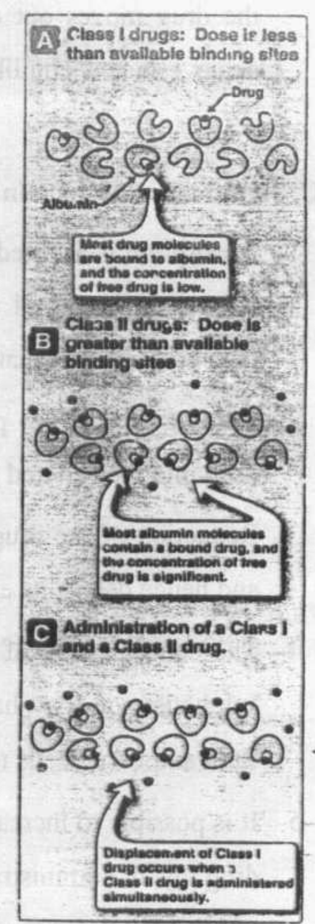


Fig. 10: Binding of Calss I and Class II drugs to albumin when drugs are administered alone (A, B), or together (C)

tolbutamide from albumin, leading to a rapid increase in the concentration of free tolbutamide in plasma, because almost 100 percent is now free compared with the initial five percent. [Note: The tolbutamide concentration does not remain elevated, because

the drug moves out of the plasma into the interstitial fluid and achieves a new equilibrium].

C. Significance of protein – binding:-

1- Absorption is assisted by binding to plasma protein and diffusion across the intestinal wall continues as the concentration within intestinal exceeds that of the free fraction in the portal capillaries.
2- Binding of drugs to plasma proteins reduces the diffusion of the drug into the cell and thereby delays its metabolic breakdown.
3- Reduction of the drug amount available for glomerular filtration and hence delays its excretion.
4- The concentration of highly protein bound drug e.g. long acting sulphonamide may be too low in interstitial fluid, cerebrospinal fluid and tissue cells to treat infections.
5- It is possible to increase the toxicity or efficacy of a highly bound drug by a administrating a second drug which has a greater affinity for the same binding sites e.g. phenandione followed by salicylates produce haemorrhage.

3-METABOLISM OF DRUGS IN THE BODY (BIOTRANSFORMATION)

Biotransformation is the various enzymatically chemical changes which a drug undergoes in the body before final elimination from the body.

The biotransformation reactions are classified into:

a) Phase one reactions, which result in an increase, change or decrease in activity.

b) Phase two reactions which usually result in drug inactivation.

a) Phase one reactions:

1- Oxidation:

The enzymes responsible are known as mixed-function oxidases. Their activity requires moleculor oxygen, NADPH (reduced nicotinamide adenine dinucleotide phosphate) and cytochrome P 450 enzymes. Some oxidations involve the removal of groups from the drug e.g. alkyl, amino and sulphur group.

Table (2): Examples of oxidative reactions undergone by drugs in the body

Reaction	**Substrate**	**Site**	**Metabolite**	**Effect on activity.**
Dealkylation	Codeine	Microsomes	Morphine	Increased
Deamiation. (MAO)	Adrenaline.	Mitochondria	Dihydroxymandelic acid.	Decreased
Desulphuration	Parathion	Microsomes	Paraoxon	Lethal
Dehydrogenation	Ethanol	Cytoplasm	Acetaldehyde	Changed

2- Reduction:-

It occurs in drugs which contain disulphide (S : S), azo (N : N) or nitro (NO_2)groups. It is the ability of animals to split the azo group as in prontosil which releases sulphanılmide in ruminants, the chloramphenicol is reduced in rumen by microflora. ($NO_2 \rightarrow NH_2$) into

inactive metabolite, so the oral route of chloramphenicol is not suitable; The chloral hydrate is, reduced and activated to trichloroethanol.

3- <u>Hydrolysis:</u>

It occurs in drugs containing ester or amide groups. The best example is hydrolysis of acetylcholine by acetylcholinesterase. Atropine is hydrolysed into ester of tropic acid and tropine in plasma, so the rabbit can consume very large amount of atropine.

Lignocaine is an amide and is more slowly degraded by a non-microsomal hepatic amidase. Digitalis is hydrolysed into oligosaccharides and aglycene of reduced activity.

b) <u>Phase two reactions:</u>

Which usually result in drug inactivation. The drugs are conjuganted with endogenous substances in the liver, kidney or gut wall.

Table (3): Examples of the groups to which conjugant substrates become attached during the metabolism of drugs.

Conjugant	**Conjugated residue**	**Drug.**
Glucuronic acid.	(O (e.g. OH)	Morphine.
	(N (e.g. SO_2 NH_2)	Sulphonamides.
Glycine	C (e.g. COOH)	Benzoic acid.
Acetyl Co A	N (e.g. NH_2)	Sulphanilamide.

In general; glucuronides and sulphate are formed most rapidly from alcohols and amines; while aromatic amines are acetylated.

Liver microsomes:

These are segments of hepatocyte endoplasmic reticulum and are obtained by ultracentrifugation of liver homogenate. Microsomal enzyme systems are accessible only to substrate with high oil-water partition coefficient. These enzymes catalyze glucuronide conjugations and most of the oxidations of drugs. Reduction and hydrolysis of drugs are catalyzed by both microsomal and non microsomal enzymes.

Factors affecting the activity of microsomal enzyme activities:

1- Sex:- Female rat metabolized drug more slowly than the male, which may be attributed to the anabolic action of the male sex hormones on drug metabolizing enzyme production.

2- Age:- The best example is increased toxicity of chloramphenicol in the young pig because of its low glucuronyl transferase activity. Faetal or newborn animals have little drug-metabolising ability.

3- Environmental temperature: The reduction of the lethal dose of amphetamine in cooled mice is an example.

4- Malnutrition: Depress the functional capacity of these enzyme systems.

5- Pathological state: Diseased liver affect its ability to metabolise drugs e.g. the action of morphine is prolonged in liver cirrhosis.

6- Animal species: Rabbits accumulate large amounts of barbiturate equal to more than twice of fatal doses and still survive without depression of C.N.S.

Induction of microsomal enzyme activity:

Repeated administration of a barbiturate results in a diminishing response, believed to be due to an increase in barbiturate metabolizing enzymes. So, the activity of the liver microsomal enzymes can be increased by administration of certain drugs.

e.g. long acting barbiturates, volatile anesthetics (ether), tranquilizers, antihistaminics, C.N.S. stimulants.

The duration of action of other drugs is decressed as in the following examples:

a) Phenobarbital stimulates the metabolism of phenytoin and dicoumarol.

b) Phenylbutazone stimulate metabolism of aminopyrine.

Inhibition of microsomal enzyme activity:

Microsomal inhibition is a feature of organophosphorus pesticides, carbon tetra chloride and chloramphenicol. It is not of importance in therapeutics, but it leads to prolongation of drug action.

Species variation in drug biotransformation:

Animal species vary in drug biotransformation depending on their variation in hepatic microsomal enzymatic activities. Young animals of all species are lacking drug metabolising enzymes.

a) Horses are rich in oxidative enzymes which shorten the duration of pentobarbitone action. They are rich also in reducing

enzymes for rapid transformation of chloralhydrate to trichloroethanol.

b) Ruminants are rich in oxidative enzymes.

c) Dogs are defecient in acetylating enzymes. The lack of an acetylase makes some compounds more toxic in dogs than in other species.

d) Cats are defecient in glucuronic acid conjugating enzymes as well as oxidative enzymes. Drugs metabolised by oxidation are cummulative and toxic in cats as barbiturates.

e) Birds have lower levels of conjugating enzymes than animals. Glucuronide conjugating enzymes are deficient in chickens.

f) Fish lack glucuronic or sulphuric acid conjugating enzymes.

4- EXCRETION OP DRUGS

Each drug is excreted from the body in a characteristic manner. Some drugs may be excreted only by a certain channal, others may be eliminated by various routes of excretion. The most important organs of excretion of drugs are the kidneys.

1. Renal excretion constitutes the most important channel for the elimination of most drugs. In the presence of renal damage, the ability of the kidneys to excrete drugs is weakened. This might result in high blood level and prolonged drug action with normal dose. Great care, therefore, must be taken when drugs as streptomycin, coumarin, etc. are used in the presence of

impaired renal function. Renal excretion is completed either by glomerular filtration, passive diffusion or active secretion.

a) Glomerular filtration depends on the glomerular blood flow, molecular size and shape of drug molecules.

b) Passive diffusion of unionized lipid soluble forms of drugs it depends on degree of ionization, lipid solubility and pk_a value and pH of the medium.

c) Active secretion of weakly acidic substances as penicillin is inhibited by probencid and prolong the antibacterial action of penicillin.

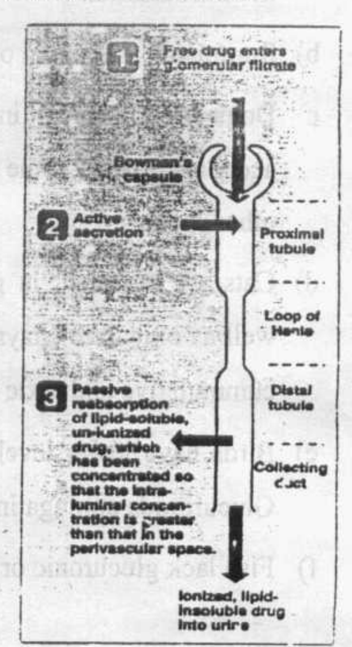


Fig. 11: Drug elimination by the kidney

2. Gaseous and volatile drugs are mainly excreted through the lungs in the inspired air. The excretion of these drugs may be impaired in the presence of diseased lung and this may cause drug toxicity.

3. Other drugs as phenolphthalein may be excreted in the bile and in this way gain access to the fasces.

4. Some other drugs as iodides and certain metallic salts may be excreted in the exocrine secretions of the body (saliva bronchial secretion and sweat).

5. During lactation, certain drugs as aloes, camphor morphine, etc., are excreted in milk.
6. Eggs are a way of excretion of some drugs such as antibiotics and coccidiostatics.

The rate of drug excretion influences the frequency of administration to maintain a constant concentration of the drug in the body. It must be noted that as drugs concentrate at the sites of excretion, they must not be given to patients with diseased organs of excretion mainly the kidneys and the lungs.

Methods of prolonging the action of drugs

The drug action can be prolonged by:-

1) Delaying drug absorption:

Absorption of drugs after oral administration can be delayed by:

a) Administration of the drug on full stomach.

b) Giving the drug in an enteric coated pill or tablet form.

Absorption of drugs after injection can be delayed by:

a) Constriction of the blood vessels of the absorbing surface:- This can be done by the administration of a vasoconstrictor drug along with the drug e.g. adrenaline when injected with the local anaesthetic procaine it prolongs its duration of ac t ion.

b) Reduction of the solubility of the drug: This can be done by:

I- Combining it with a poorly soluble substance e.g. penicillin is combined with procaine

II- Giving the drug in a suspension form e.g. watery suspension of testosterone.

c) Administration of the drug in oily solution: Gonadal hormones are usually used in oily solution e.g. progesterone oily injections.

d) Combination of the drug with protein: This cause the drug to be released slowly from this combination e.g. insulin is combined with protamin in the form of protamine zinc insulin to prolong its action.

e) Estrification of certain drugs e.g. oestrogens or progesterones when estrified with benzoic or propionic acid forming oestradiol monobenzoate or progesterone dipropionate respectively which are slowly absorbed.

f) Implantation of the drug pellets (Implants) subcutaneously: e.g. stilboesterol implants. This ensure slow and prolonged absorption.

2) Delaying drug metabolism in the liver: The microsomal enzyme systems concerned with biotransformation of drugs in the liver may be depressed by starvation or destruction of liver cells by certain drugs (enzyme inhibitors) such as SKF 525 A, largactil, etc. Inhibiting the activity of these microsomal enzymes (which detoxify drugs) leads to prolonged drug action.

3) Increased protein binding of the drug in the plasma: Certain drugs can be prepared in compounds which are bound to plasma protein than other compounds of the original drug e.g. long acting sulphonamides (as sulphamethoxypyridazine) are bound to protein

much more extensively than the short acting sulphonamides (as sulphadiazine).

4) Delaying renal excretion: Excretion of drugs can be reduced by blocking glomerular filtration or by suppressing renal reabsorption as probenecid.

Relationship between chemical structure and pharmacological action of drugs

Substances of similar chemical configuration with certain organic drugs as adrenaline, atropine, caffeine, etc., are synthesized by drug chemists. These synthetic drugs have similar pharmacological actions to the original drugs. But, there are certain drugs-with similar chemical structure to some endogenous substances-which have an antagonistic or opposite actions in the body such as the antagonism between histamine and the antihistaminic drug, benedryl which react with the same receptors and prevent the access of histamine to the cell many drugs loose their activity if any change is made in the configuration of the drug molecules, whereas, other drugs with totally different chemical structures may possess similar actions e.g. aloes and magnesium sulphate which have purgative effect although they differ chemically.

Drug derivatives

Drug chemists always make trials to prepare valuable derivatives from drugs. Synthesis of new drug derivatives may be required for the following purposes:

1) To increase or decrease the duration of action of the original drug or to get a more potent compound e.g. homatropine causes shorter duration of mydriatic effect than atropine.

2) To localise the drug action to a peculiar part of the body e.g. apomorphine has a localised action on the vomiting center and possesses negligable depressant effect of morphine on the central nervous system.

3) To reduce the side effects, toxicity or other disadvantages of the original drug e.g. phenoxymethyl penicillin is not destroyed in the stomach as crystalline penicillin so it a can be administered by mouth while crystaliine penicillin cannot.

DRUG RESIDUES

Heavy responsibility is placed on the veterinarian and livestock producer to observe the period for withdrawal of a drug prior to slaughter to assure that illegal concentrations of drug residues in meat, milk and eggs do not occur. Greater attention from a public health aspect has centered on the safety of tissue residues as a result of increased use of veterinary drugs and the extensive use of chemical in the food supply.

The following terms are commonly used by pharmacologist, toxicologists and regulatory officials.

Drug or chemical residue:

A residue of a parent drug or chemical and its metabolites may accumulate and be deposited or stored within the cells, tissues or

organs of an animals following the use of drugs or chemicals or feed additive. Residual quantities of a drug or chemical and its derivatives are expressed in parts by weight such as mg / kg or mg / L (i.e. ppm) or μg / kg or μg / L (i.e. ppb) or ng / kg or ng / L (i.e. ppt).

Feed additives:

Feed additives are defined as drug, chemical or biologic substances added directly to animal feeds in small quantities to modify some aspect of performance or production.

Target animal:

Use of target animal refers to the determination of safety and efficacy of a drug directly within the species for which therapeutic uses are made by the drug manufacturer.

Unintentional residue:

It is one that occurs in a feed or food as a result of circumstances not intended to protect the feed or food against the attack of infectious or parasitic diseases.

Acceptable daily intake (ADI):

It is the daily dose of a drug or chemical residue that during the entire lifetime of a person appears to be within appreciable risk to health.

Tolerance level:

It is the maximum allowable level or concentration of a drug or chemical in or on feed or food at a specified time of slaughter and till the time of consumption by animal or human. It is expressed in parts by weights of drug / million (mg/kg) or billion (mg/kg) of the food. There are 3 major types of tolerances:-

a) Finite tolerance: It is defined as a measurable amount of drug or chemical (noncarcinogen) residue that is permitted in food.

b) Negligible tolerance: A toxicologically insignificant amount of residue, resulting in a daily intake that is a small fraction of the maximum ADI.

c) Zero tolerance: Zero tolerances are determined on the basis that no residue is permitted in feed or food because of extreme toxicity or most after because the compound is carcinogenic.

d) Temporary tolerance: It is one that is valid for a restricted period and subject to revision upon availability of new information.

The equation for establishing a tolerance level is:

$$\text{Tolerance} = \frac{\text{ADI} \times 60\ \text{kg}}{\text{Food factor} \times 1.5\ \text{kg/day}}$$

ADI : acceptable daily intake.

60 kg : human body weight.

1.5 kg : total daily dietary intake of 1.5 kg solid food or 1.5 L milk.

Food factor: It is used by the FDA as guidelines in deriving a tolerance level. Table (4) presents food or consumption factors for tissues in relation to skeletal muscle.

Table 4: Consumption or food factors relative to muscle.

Tissue	Beef	Sheep	Poultry
Muscle	1	1	1
Liver	2	5	3
Kidney	3	5	5
Fat.	4	5	2

Tolerances are established for noncarcinogenic compounds. Many chemical substances and drugs act a hazard residues in human food stuffs e.g.:

1- Some impurities as nitrates, nitrites heavy metals, chlorinated hydrocarbons and aflatoxins.

2- Some additives as colours, flavouring agents, bleaching agents antioxidants and additives to animal food.

3- Veterinary drugs as chemotherapeutic agents, hormones,...etc. Residues of chemicals or drugs produce **toxic or undesirable effects** when they are consumed in human food at a level higher than the permissible limits. These effects are:

1- Carcinogenic effects : It refers to an effect produced by a substance e.g hormones and aflatoxins having a cancer-producing activity.

2- Mutagenic effect: The term mutagen is used to describe chemical agents that damage the genetic components of a cell or organism.

3- Teratogenic effect: The term teratogen applies to drug or chemical agents that produce a toxic effect on the embryo or fetus during a critical phase of gestation.

4- Drug allergy or hypersensitivity: An allergic or hypersensitive effect following administration of a drug (i.e. drug allergy) is similar to that typified by allergic responses to protein, carbohydrate and lipid macromolecules. Allergic reactions to drugs or chemicals may include anaphylaxis, serum sickness and cutaneous reactions.

Withdrawal times and tolerances for veterinary drugs:

The withdrawal time (also known as the depletion or clearance period) is the time required for the residue of toxicologic concern to reach safe concentration as defined by the tolerance. It also refers to the interval from the time an animal is removed from medication until the permitted time of slaughter. This interval is required to minimize or prevent violative levels of drug residues in edible tissues for human consumption. Withdrawal time intervals vary with each drug preparation and among the different species. Depending on the drug product, dosage form, and route of administration, the withdrawal time may vary from a few hours to several days or weeks.

Table (5): Withdrawal times (W.T.) and tolerance levels (T.L.) of drugs in animals following parentral and oral administrations:

(A) Cattle.

Drug	Paranteral administration		Oral administration	
	W.T. (days)	T.L. (ppm)	W.T. (days)	T.L. (ppm)
*Ampicillin trihydrate	6	M&MK 0.01	15	M, 0.01
*Amprpluim	-	-	1	F, 2. M, L&K,0.5;
*Bacitracin	-	-	0	M&MK, 0.05
*Chloroteracyline (11 mg/kg/day)	-	-	10	M, 0.1:F&MK,0
*Chloroteracycline (350mg/head/day)	-	-	2	M,K.L.0:F&MK 0.
* Dihydrostreptomycin	30	M & MK, 0	10	M . 0
* Erythromycin	14	M & MK, 0	-	-
* Furosemide	2	Non published	2	non published
* Halaxon	-	-	7	M, 0.1
*Levamisol hydrochloride	7	M, 0.1	2-3	M, 0.1
*Lincomycin	-	MK. 0.15	-	-
Oxytetracycline. hydrochloride.	22	M, 0.1	7	M, 0.1
* Procaine penicillin G.	10	M, 0.05, MK, 0.	-	-
*Streptomycin	-	-	2	M,0.

*Sulpabromomethazine	-	-	10	none published
*Sulphmethazine	10	M, 0.1	21	M, 0.1
Sulphachloropyridazine Soduim.	5	M, 0.1	7	M, 0.1
*Tetracycline.	-	-	5	M, 0.25
* Thiabendazole.	-	-	5	M, 0.1, MK 0.05

M: Meat. K: Kidney L. Liver

F: Fat MK: Milk

Table (5): (Continued):

(B) Sheep and goat.

Drug	W.T. (days)	T.L. (ppm.)
<u>1) Injectable drugs:</u>		-
*Erythromycin	3	-
* Dihydrostreptomycin	30	M , 0
*Procain penicillin G	9	-
*Sulfamethazine	10	-
<u>2- Oral drugs:</u>		
* Chlortetrocycline	2	-
*Haloxon.	7	M, 0.1.
*Levamisol hydrochloride	3	M,0.1.
*Sulfamethazin	10	-
*Tetracyline	-	M,0.25
*thiabendazole	30	M,0.1

(C) Chickens		
*Amprolium	0	L, K, 1; M, 0.5; whole eggs, 0.5.
*Bacitracin	0	M, eggs, 0.05.
Chlorotetracycline	1	K, 4; M, L, F, 1, eggs, 0.
Erythromycin.	1 – 2	eggs, 0.025.
*Estradial monopalmitate.	42	M, 0.
*Furazolidone	5	-
*Gentomycin, injection	35	-
*Hineomycin	5	M, 0.1.
*Novobiocin	4	M, 0.
*Oxytetracyline	0	K, 3; M, L, F, 1.
*Penicillin.	1	M, 0.
*Spectinomycin.	5	M, 0.1.
*Streptomycin	4	M, 0.
*Sulphadimethoxone	5	M, 0.1.
*Sulphaquinoxaline	10	-
*Tylosin	5	eggs, 0.2.

M: Meat. K: Kidney L:Liver.

F: Fat MK: Milk

II. DRUGS ACTING ON THE AUTONOMIC AND SOMATIC NERVOUS SYSTEMS

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The autonomic nervous system is a peripheral complex of efferent and afferent nerves, plexuses and ganglia that modulate the involuntary activity of secretory glands, smooth muscles and visceral organs. Historically, this system also has been termed the visceral, involuntary or vegetative nervous system. The autonomic nervous system reacts to maintain respiration, heart rate, blood pressure, gastrointestinal activity, urinary output and virtually all other visceral functions within well-defined physiologic limits. In addition, autonomic activity can rapidly increase or decrease in response to sudden changes in the environment.

Organization of the autonomic nervous system:

The most important components of the autonomic nervous system, in relation to clinical pharmacology, are the outflow (efferent) nerve tracts. Efferent autonomic tracts supply motor innervation to visceral structures. The efferent segment of the autonomic nervous system is divided into two principal components, the sympathetic nervous system and the parasympathetic nervous system. A schematic representation of the sympathetic and parasympathetic outflows is shown in Fig. (12).

Sympathetic and parasympathetic outflow tracts comprise preganglionic neurons and postganglionic neurons. The cell body of a preganglionic neuron is located within the central nervous system. The synapse (junction) of a postganglionic axon with a postganglionic neuronal body occurs outside the central nervous system within an autonomic ganglion.

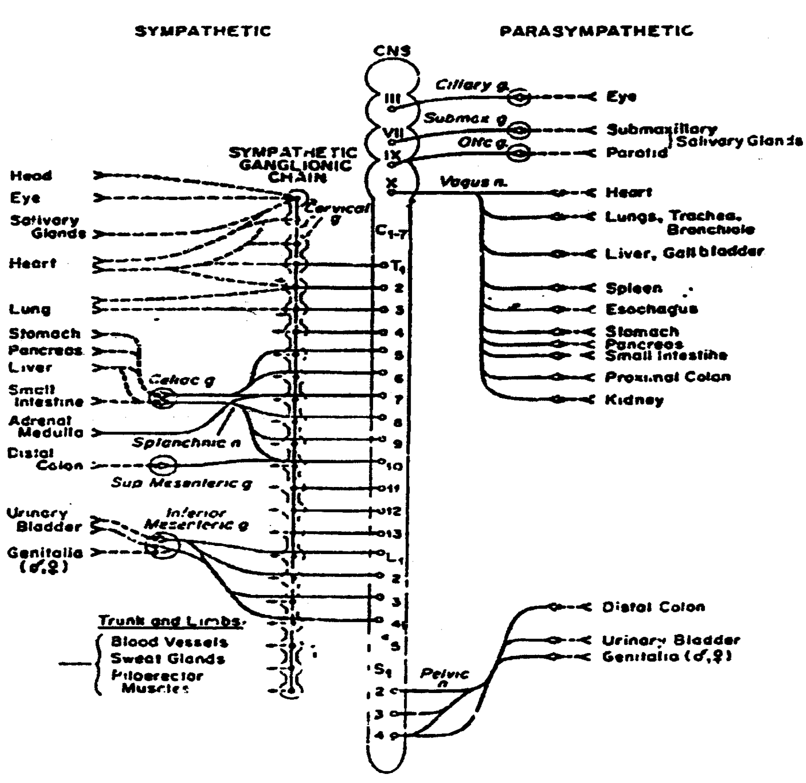


Fig.(12): Schematic representation of sympathetic and parasympathetic motor innervation of various body organs.

Autonomic ganglia are specialized nodular structures comprising numerous (100,000) neuronal bodies. An axon of a postganglionic cell passes peripherally and innervates its effector organ or organ substructure. The junction of a postganglionic axonal terminal with its effector cell is termed a neuroeffector junction.

Sympathetic nervous system:

The sympathetic nervous system is synonymously referred to as the thoracolumbar outflow because of the anatomic origin of this system. Sympathetic preganglionic fibers (axons) originate from cell bodies localized within the intermediolateral columns of the thoracic and lumber regions of the spinal cord.

Paravertebral (or vertebral) ganglia are located bilaterally to the ventral aspects of the vertebral column. Ganglia on each side are interconnected by nerve fibers to form the sympathetic gang ionic chain, which extends into the cervical and sacral regions; however, ganglia in these areas receive fibers only from the thoracolumbar spinal cord.

Sympathetic postganglionic fibers are usually relatively long since most sympathetic ganglia are located in close proximity to the spinal cord. One sympathetic ganglionic neuron may be innervated by preganglionic fibers originating from several different nerve bodies.

Parasympathetic nervous system:

Parasympathetic outflow tracts originate from the midbrain, medulla oblongata and sacral spinal cord. The parasympathetic

component of the autonomic nervous system is therefore referred to anatomically as the craniosacral outflow.

The cranial portion of the parasympathetic system comprises nerve fibers arising from the 3rd, 7th, 9th, 10th and 11th cranial nerves, while the sacral portion of the parasympathetic system arising from the sacral spinal cord.

Parasympathetic ganglia are localized peripherally than sympathetic ganglia and are close to or within innervated organs. Accordingly, postganglionic parasympathetic fibers are usually quite short.

General concepts of autonomic function:

Many visceral organs are innervated by both parasympathetic and sympathetic division (Fig. 12), with each producing contrasting effects on the same structure.

Principal organ responses mediated by sympathetic and parasympathetic discharge are summarized in Table (6).

Neurohumoral transmission:

The neurotransmitter at all ganglia (both parasympathetic and sympathetic) and at parasympathetic neuroeffector junctions is acetylcholine (ACh). In a few regions e.g. erectile tissue of genitalia, the parasympathetic neurotransmitter at neuroeffector junctions does not seem to be ACh. Norepinephrine (noradrenlaline) is the transmitter released at the majority of sympathetic neuroeffector junctions and is considered as sympathetic neurotransmitter. At a few sympathetic

neuroeffector junctions e.g. sweat glands and blood vessels of the face in man, ACh is the transmitter.

Table (6): Responses of effector tissues to sympathetic and parasympathetic nerve impulse.

Effector tissues	Sympathetic-mediated responses	Parasympathetic-mediated responses
Heart	General excitation	General inhibition
Sinoatrial (SA) node	β_1 increase heart rate	Decrease heart rate
Atria	β_1 increase contractile force, conduction velocity	Decrease contractile force
Atrioventricular (AV) node	β_1 increase automaticity, conduction velocity	Decrease conduction velocity; AV block
His-Purkinje system	β_1—increase automaticity, conduction velocity	
Ventricles	β_1 increase contractile force, conduction velocity, irritability	Decrease contractile force
Blood vessels		
Coronary	α constriction; β—dilation	Dilation ; constriction
Cutaneous, mucosal	α—constriction	Dilation
Cerebral	α—constriction; β—dilation	Dilation
Skeletal muscle	α—constriction; β_2—dilation	Dilation
Splanchnic	α—constriction; β_2—dilation	Dilation
Renal	α—constriction; β_2—dilation	Dilation
Genital	α—constriction	Dilation
Veins	α—constriction	...
GI tract	General inhibition	General excitation
Smooth muscle	β_2 - relaxation; α—relaxation	Increase motility and tone
Sphincters	α -contraction	Relaxation
Secretions	Decrease (usually)	Increase
Gallbladder and ducts	Relaxation	Contraction
Bronchioles		
Smooth muscle	β_2—relaxation	Contraction
Glands	Inhibition (?)	Stimulation
Eye		
Pupil	α—mydriasis	Miosis
Radial muscle, iris	α—contraction	...
Sphincter muscle, iris	...	Contraction
Ciliary muscle	β relaxation (?); far vision	Contraction; near vision
Urinary bladder	Urinary retention	Urination
Fundus	β_1 relaxation	Contraction
Trigone, sphincter	α contraction	Relaxation
Splenic capsule	α—contraction, β—relaxation	...
Sweat glands	Secretion (cholinergic); α—secretion (horse)	...
Salivary glands	α—scant, viscous secretion	Profuse, watery secretion
Piloerector muscles	α—contraction	...
Kidney renin release	α—decrease; β_1—increase	...
Uterus	α—contraction; β—relaxation (nonpregnant > pregnant)	Contraction
Genitalia		
Male	α—ejaculation	Erection
Female	...	Erection
Adrenal medulla	Secretion of epinephrine > norepinephrine (cholinergic)	...
Autonomic ganglia	Ganglionic discharge (cholinergic)	Ganglionic discharge
Liver	β_2—glycogenolysis and gluconeogenesis (α in some species)	...
Pancreas		
Islet cells	α—decrease secretion; β—increase secretion	...
Acini	α—decrease secretion	Increase secretions
Fat cells	β_1— lipolysis	...
Adrenergic nerve terminals	α—decrease release of norepinephrine β—increase release of norepinephrine	± Release of norepinephrine

Nerves that release ACh are classified chemically as cholinergic nerves. Nerves that release norepinephrine are classified chemically as adrenergic nerves. Preganglionic and postganglionic relationships of sympathetic and parasympathetic efferent fibers are shown in Fig. (13). An adrenergic nerve releases norepinephrine and is a sympathetic preganglionic nerve. A cholinergic nerve releases ACh but can be parasympathetic and sympathetic preganglionic nerves; a parasympathetic postganglionic nerves and a sympathetic postganglionic nerve (in few regions).

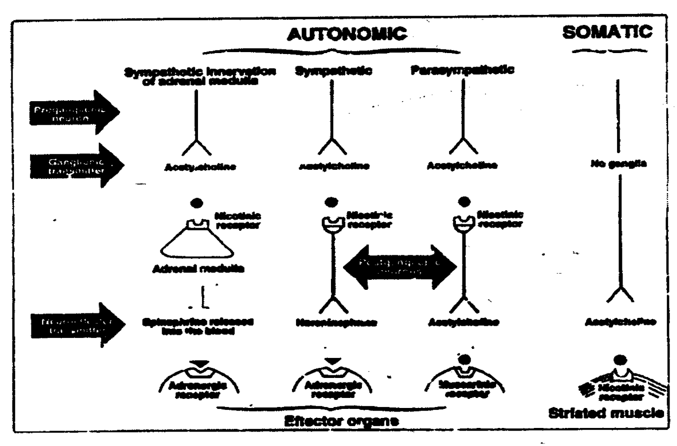


Fig. 13: Summary of the neurotransmitters released and the types of receptors found within the autonomic and somatic nervous systems. [Note: this schematic diagram does not show that the parasympathetic ganglia are close to or on the surface of the effector organic and that the postganglionic fibers are usually shorter than the preganglionic fibers. By contrast, the ganglia of the sympathetic nervous system are close to the spinal cord. The postganglionic fibers are long, allowing extensive branching to innervate more than one organ system. This allows the sympathetic nervous system to discharge as a unit].

Virtually every autonomic drug that is clinically used exerts its primary pharmacologic activities by altering some essential step(s) in the neurohumoral transmission process.

Neurohumoral transmission at ganglionic synapses and neuroeffector junctions can be subdivided into axonal conduction, synthesis & release of the neurotransmitter, receptor events and catabolism of the neurotransmitter.

1. Axonal conduction:

It refers to the passage of an impulse along a nerve fiber. At rest, membrane potential within mammalian axons is approximately -85 mV. This negative intracellular potential is maintained at rest basically because the axonal membrane is relatively more permeable to K^+ than to Na^+. Na^+ are in higher concentration in extracellular than in intracellular fluid, whereas K^+ are in greater concentration in intracellular than in extracellular fluid. The small amounts of K^+ that leak into the interstitial space and large amounts of organic anions that are intracellular result in a net negative charge within the axon.

An action potential represents a reversal of the polarization state present at rest and is therefore a depolarization process. A suprathreshold stimulus initiates localized change in the permeability of the axonal membrane. Suddenly, permeability of the fiber to Na^+ is greatly increased in relation to K^+; Na^+ moves inward in the direction of its large electrochemical gradient. The positive charged Na^+ increase in concentration within the axon; the membrane potential moves from -85 mV toward zero and then overshoots to the extent that momentarily the inside of the fiber is positive in relation to the exterior of the cell.

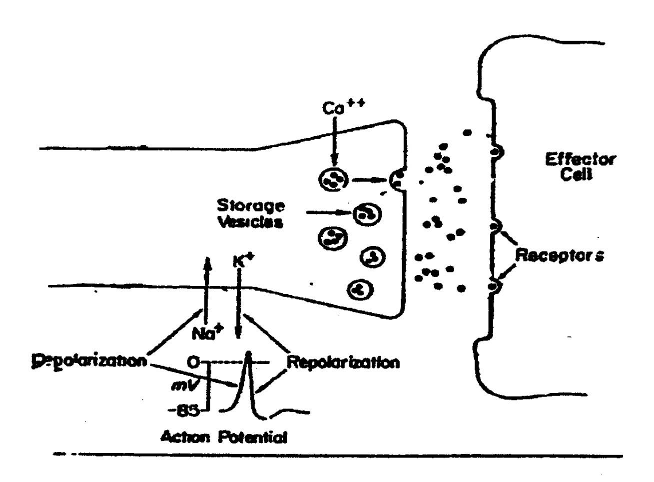


Fig. (14): Schematic representation of neurohumoral transmission.

Repolarization of the membrane occurs rapidly as the selective permeability characteristics of the axonal membrane are quickly re-established. The axon once again becomes relatively impermeable to Na^+ and relatively more permeable to K^+, and the negativity of the interior of the cell is quickly reestablished (Fig.14).

Although the localized permeability changes associated with an action potential are extremely short-lined, they elicit similar alterations in membrane function in adjacent areas of the axon. Thus the action potential is self propagating and an action potential is conducted along an axonal fiber.

2. Neurotransmitter release:

Release of neurotransmitter substance is triggered by arrival of the axonal action potential at the nerve terminal (Fig. 14) where neurotransmitters are stored in vesicular structures. Ca^{++} act to link or couple the excitation of the membrane (action potential) with discharge of neurotransmitter from the nerve terminal. The action potential initiates an inward movement of Ca^{++} into the nerve terminal from the interstitial space and/or membrane binding sites. Inward movement of Ca^{++} helps the discharge of neurotransmitter from the vesicles into the junctional cleft.

3. Receptor events:

Receptor events caused by interaction of transmitter substance with the receptor may be of two general types, excitatory or inhibitory. If the neurotransmitter initiates an excitatory response in the cell, receptor activation triggers a general increase in permeability of the postsynaptic membrane to all ions and consequently postsynaptic nerve action potential occurs along the remainder of the innervated cell.

An inhibitory postsynaptic when the neurotransmitter initiates a selective increase in permeability of the postsynaptic membrane to only smaller ions (e.g. K^+, Cl^-). Thus outward movement of K^+ and inward movement of Cl^- along their respective concentration gradients increase the net negative charge within the cell and actually hyperpolarize the postsynaptic membrane. The resulting hyperpolarization of the membrane increases the threshold to stimuli and, in effect, elicits an inhibitory response in the cell.

The binding of chemical signals to receptors activates enzymatic processes within the cell membrane that ultimately result in a cellular response, such as the phosphoryiation of intracellular proteins or changes in the conductivity of ion channels. A neurotransmitter can be thought of as a signal and a receptor as a signal detector and transducer. "Second messenger molecules" produced in response to neurotransmitter binding to a receptor, translate the extra cellular signal into a response that may be further propagated or amplified within the cell. Each component serves as a link in the communication between extracellular events and chemical changes within the cell.

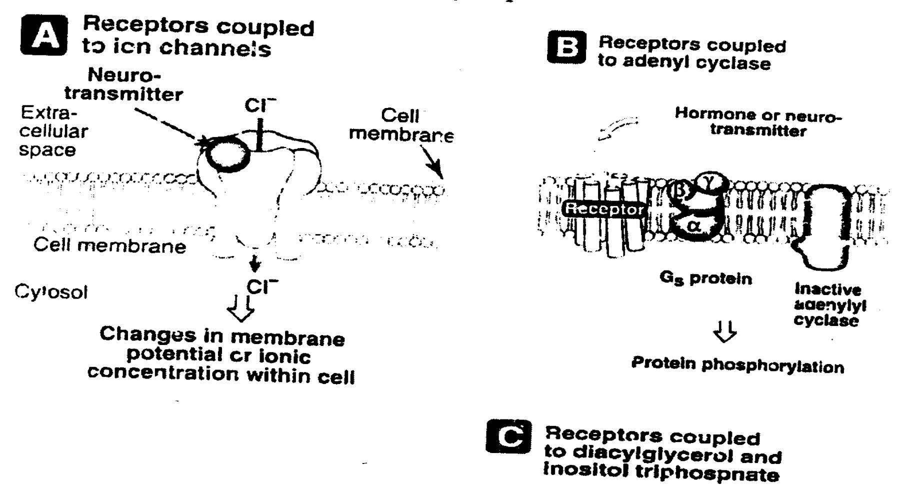
A. Membrane receptors affecting ion permeability

Neurotransmitter receptors are membrane proteins that provide a binding site that recognizes and responds to molecules. Some receptors, such as the postsynaptic receptors of nerve or muscle, are directly linked to membrane ion channels; thus, binding of the neurotransmitter occurs rapidly (within fractions of a millisecond) and directly affects ion permeability (Fig. 15)

B. Regulation involving second messenger molecules

Many receptors are not directly coupled to ion gates. Rather, the receptor signals its recognition of a bound neurotransmitter by initiating a series of reactions, which ultimately results in a specific intracellular response. "Second messenger" molecules—so named because they intervene between the original message (the neurotransmitter or hormone) and the ultimate effect on the cell—are part of the cascade of events that translates neurotransmitter binding

into a cellular response, usually through the intervention of a G protein. The two most widely recognized second messengers are the adenylyl cyclase system and the calcium/phosphatidylinositol system (Fig 15-B and -C). [Note: G_s is the protein involved in the activation of adenylyl cyclase and G_q is the subunit that activates phospholipase C to release diacylglycerol and inositol triphosphate.



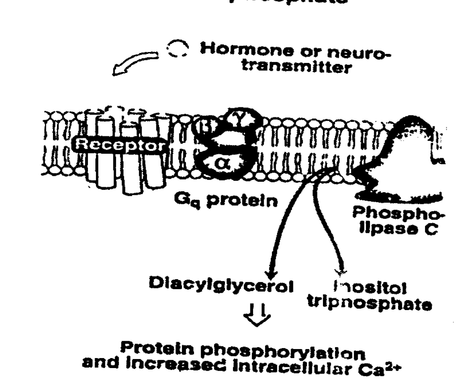


Fig. 15 (A, B, C): Three mechanisms whereby binding of a neurotransmitter leads to a cellular effect.

4. Catabolism of neurotransmitter:

Norepinephrine is metabolized by both intraneuronal and extraneuronal enzymes. The uptake of norepinephrine back into the adrenergic nerve terminal, and diffusion away from receptor sites are more important pathways for termination of norepinephrine activity. Extraneuronal ACh is rapidly hydrolyzed by acetyl cholinesterase.

Autonomic receptors:

These are areas on the surface of the effector cells. Each group of receptors is supposed to combine specifically with the chemical transmitter. Hence receptors are classified into:

a) **Adrenergic receptors:** (Adrenoceptors) which respond to adrenaline and noradrenaline. The adrenoceptors have been subdivided into alpha (α) and beta (β) receptors. Noradrenaline is a powerful agonist at alpha adrenoceptors. The adrenoceptors in the smooth muscle of the blood vessels are called now adrenoceptors. Those α, adrenoceptors on prejunctional membrane e.g. adrenergic neurons are now called α_2 adrenoceptors. They are stimulated selectively by clonidine. The established α blockers block both α_1 and α_2 adrenoceptors. The β adrenoceptors are subdivided into β_1 and β_2. The β_1 receptors are found in the heart and intestine, while those found in smooth muscle of bronchi, vasculature and uterus are called β_2 adrenoceptors. Isoprinaline is a mixed and agonist. Salbutamol is a β_2 agonist. Adrenaline is an agonist of both α and β adrenoceptors.

b) **<u>Cholinergic receptors</u>**: (cholinoceptors) which respond to acetylcholine. The action of acetylcholine on the peripheral cholinergic receptors is blocked by atropine while that on the central receptors is blocked by large doses of nicotine.

Autonomic drugs

Autonomic drags are classified according to the physiologic activity they mimic. Table (7) summarizes the classification of the basic types of autonomic drugs.

Table (7): Classification of autonomic drugs.

Classification	Other terms	Pharmacologic effects	Mechanisms and examples
Sympathomimetic	Adrenergic Adrenomimetic	Resemble effects caused by stimulation of adrenergic neurons Simulate effects of epinephrine and norepinephrine	Direct acting—α,β-adrenergic receptor agonists (α-phenylephrine; β-isoproterenol; α,β-epinephrine) Indirect acting —release endogenous stores of catecholamines (tyramine, amphetamine) Increase sympathetic discharge—nicotinic cholinergic agonists)
Sympatholytic			
Receptor blocking effects	Adrenergic blocking drugs	Inhibit effects of sympathomimetic drugs; inhibit responses caused by stimulation of adrenergic neurons	Block α or β receptors (α blocker—phentolamine; β blocker—propranolol)
Neuronal blocking effects	Adrenolytic	Inhibit responses caused by stimulation of adrenergic neurons	Deplete endogenous catecholamines (reserpine) Inhibit release of norepinephrine from nerve terminals (bretylium)
Parasympathomimetic	Cholinergic Cholinomimetic	Resemble effects caused by stimulation of postganglionic parasympathetic neurons Simulate effects of ACh	Direct acting—cholinergic receptor agonists (ACh, carbachol) Indirect acting—cholinesterase inhibitors (neostigmine, organophosphates)
Parasympatholytic			
Receptor blocking effects	Cholinergic blocking drugs	Inhibit effects of ACh; inhibit responses caused by stimulation of postganglionic parasympathetic neurons	Block nicotinic or muscarinic receptors (muscarinic blocker—atropine; nicotinic blocker—hexamethonium)
Neuronal blocking effects	Anticholinergic	Inhibit responses caused by stimulation of postganglionic parasympathetic neurons	Inhibit release of ACh from nerve terminals (botulinum toxin)

Adrenergic drugs

These are drugs which act on the adrenergic receptors (α and β). They are referred to as sympathomimetic agents in reference to their mimic of sympathetic nervous system activity. Sympatholytic, adrenolytic and adrenergic blocking drugs exert pharmacologic effects that simulate a decrease in adrenergic nerve activity.

Sympathomimetics (adrenomimetics)

These are drugs which stimulate the adrenoceptors in plain muscles, cardiac muscle and exocrine glands.

Classification: Adrenomimetics are classified according to their chemical structure into:

1) Catecholamines:

These contain the catechol nucleus in their chemical structures e.g. adrenaline, noradrenaline, isoprenaline and dopamine.

2) Non catecholarnines:

These do not contain catechol nucleus in their chemical structures e.g. ephedrine, amphetamine and tyramine.

Mechanism of action of adrenornimetics:

Sympathomimetics stimulate the adrenergic nervous system through the following:

a) Direct stimulation of α or β receptors as adrenaline, nor adrenaline and isoprenaline.

b) Indirect stimulation by the release of catecholamines from their stores at nerve endings as amphetamine and tyramine.

c) Dual mechanism i.e. by direct and indirect ways as ephedrine.

I- CATECHOLAMINES

1- Adrenaline: (Epinephrine)

synthesis

Adrenaline is synthesized from the amino acid. phenylalanine in a stepwise process as summarized in Fig. (16).

Fig. (16): The biosynthesis pathway of norepinephrine and epinephrine.

Storage, release, reuptake and metabolism:

Storage of adrenaline within the granular vesicles is accomplished by the complexation of the catecholamine with adenosine triphosphate (ATP) and a specific protein, chromogranin. This complexation renders the amines inactive until their release. The amine storage process represents a net result of several functional interrelations e.g., the intragranular pool of norepinephrine consists of ATP-protein complex (as reservoir) and of more mobile pool. Catecholamines are taken up from the cytoplasm into the granules by

an active transport system that is ATP and Mg^{++} dependent. The cytoplasmic amine pool is not bound. Amines within the cytoplasm may be taken up by the granules for storage or inactivated by monoamine oxidase (MAO). Intracytoplasmic dopamine may be deaminated by MAO (Fig. 17, Fig. 18 and Fig. 19).

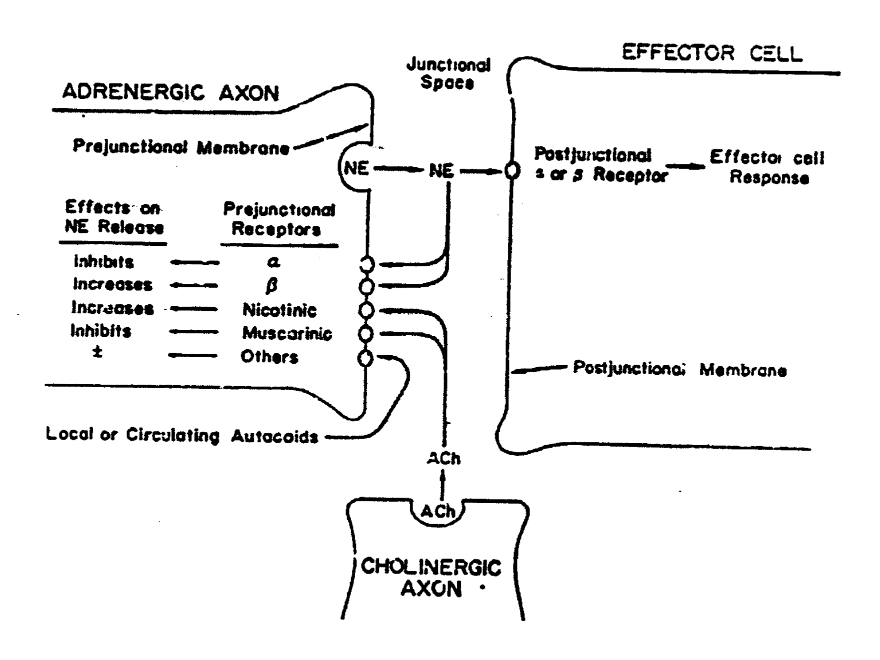


Fig. 17

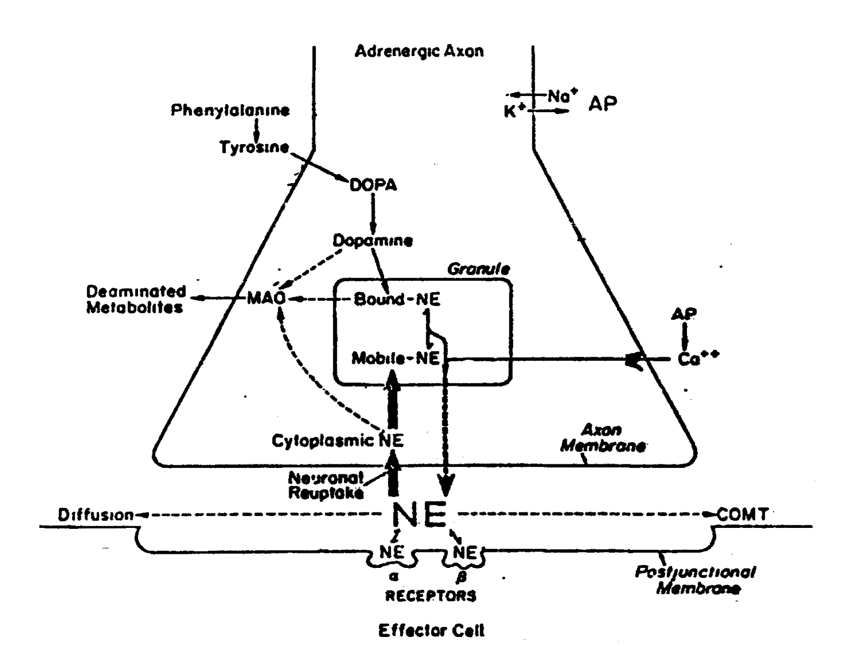


Fig. 18

In the adrenal chromaffin cells, ACh released from the preganglionic axon acts on specific receptors, resulting in depolarization of the membrane. Which enhances the influx of Ca^{++}. This later process results in the discharge of granular constituents into the interstitial fluid, then into the circulation. Released norepinephrine interacts with specific adrenergic receptor sites on the postjunctional membrane.

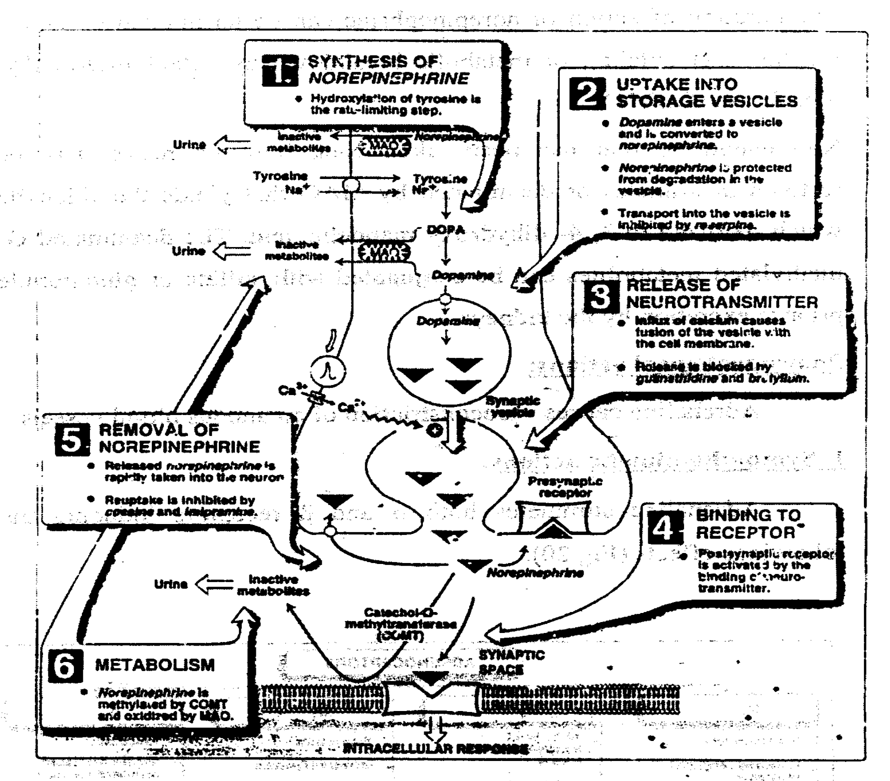


Fig. (19): Synthesis and release of norepinephrine from the adrenergic neuron.

The adrenergic neuronal uptake mechanism in referred to as $uptake_1$, $uptake_2$ signifies the extraneuronal uptake of catecholamines into surrounding tissue, its physiological significance is not known.

The duration of action of norepinephrine can be terminated by active reuptake via uptake$_1$, or metabolic breakdown by catechol-O-methyl transferase (COMT).

Norepinephrine that has been taken back into the nerve may be restored in granules or deaminated by MAO that yields the aldehyde which oxidized to 3, 4- dihydroxy mandelic acid. The deaminated O-methylated metabolites can be conjugated with sulfate or glucuronide prior to excretion by the kidneys.

Pharmacological actions:

Adrenaline causes vasoconstriction of cutaneous blood vessels.

1. Sympathomimetic actions:

Adrenaline stimulates both α and β receptors inducing the followings effects (Fig 20).

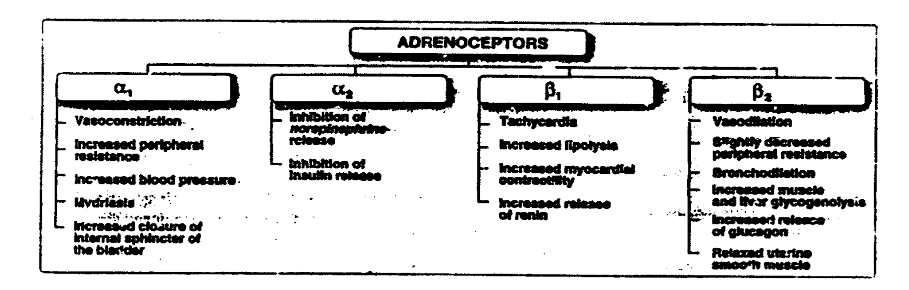


Fig. (20): Major effects mediated by α and β receptors.

a) It increases the force (positive inotropic) and rate of cardiac contractility (positive chronotropic). Catecholamines enhance the

influx of Ca^{++} into the myocardial cell as a result of increase concentration of intracellular AMP. This increase in concentration of cAMP results from increase in the activity of adenylate cyclase enzyme by adrenaline. Further, cAMP activates phosphorylase, resulting in glycogenolysis and increased energy availability.

b) Adrenaline is very potent constrictor of cutaneous and mucosal blood vessels in mammalian species (α receptor), but it produces vasodilatation of skeletal and coronary blood vessels (β_2 receptor).

c) Adrenaline increases the blood pressure as a result of increased cardiac output and peripheral resistance.

d) It is a potent bronchodilator as a result of relaxation of bronchial smooth muscle (β_2).

e) Adrenaline causes relaxation of the intestinal muscle and contraction of sphincters (α).

f) It relaxes the ditrusor muscle of the urinary bladder (β_2) and contracts the sphincter (α) which results in urine retention.

g) The effect of adrenaline on uterine muscle varies according to species and stage of the estrous and gestational cycles. Adrenaline relaxes the uterine muscle of guinea pig, rat and non-pregnant cat but contract the uterine muscle of rabbit, bitch and pregnant cat.

h) Adrenaline contracts the splenic capsule (α).

i) It dilates the pupils (mydriasis).

j) It inhibits the exocrine gland secretions and gives scanty mucous saliva.

2- Metabolic action:

Adrenaline induces the following effects on metabolism:

a) Glycogenolysis.

b) Increase the blood lactate and free fatty acids.

c) Increase the basal metabolic rate.

3- Adrenaline stimulates the release of ACTH which enhance cortisone and hydrocortisone production.

4- Epinephrine facilitates neuromuscular transmission so hasten recovery from fatigue (α effect).

5- Adrenaline acts as antihistaminic and antiallergic.

6- It accelerates the blood coagulation.

7- Adrenaline has a weak effect on central nervous system and may causes restlessness and tremors.

Therapeutic uses:

1. Acute bronchial asthma.
2. Allergy, hypersensitivity and anaphylactic shock. (0.5 – 1 ml, 1/1000 solution.
3. Adrenaline is used with local anaesthetics, in concentration of 1-20,000 – 1/100,000.
4. Cardiac arrest.
5. Hypoglycaemia.
6. Epistaxis as local haemostatic in concentration of 1/2000 — 1/50000.

Adrenaline is **contraindicated** in coronary diseases, hyperthyroidism, hypertension and general volatile anaesthetics.

2. Nor adrenaline:

Noradrenaline affect mainiy α receptors. It causes vasoconstriction in muscles, skin and viscera resulting in rise of blood pressure. This rise in blood pressure stimulates the vagus resulting in bradycardia. The smooth bronchial muscles are not affected (β_2) while the intestine is relaxed (α/β).

Noradrenaline is used as a hypertensive in spinal anaesthesia and post operative collapse, 2 mg in 1 liter glucose (i.v.).

3. Isopropyl noradrenaline: (isoprenaline):

Isoprenaline mainly affects β receptors increasing the cardiac rate and force of contraction, cardiac excitability (s.a. and A.V. nodes, bundle of his and purkinje fibers), and cardiac output (β_1). It dilates the

blood vessels in muscles, skin and coronaries decreasing the blood pressure (β_2). It relaxes the bronchial (β_2) intestinal and uterine muscles.

Therapeutic use: Acute bronchial asthma and heart failure. dose: 5-20 mg.

4. **Dopamine:**

$$HO-C_6H_3(OH)-CH_2-CH_2-NH_2$$

It is precursor of **noradrenaline. It is present in the brain,** hypothalamus, **basal ganglia, used for the treatment of parkinsonism** given as 1-dopa as **the brain is impermeable to dopamine.**

5. **Dobutamine:**

- **Actions:** Dobutamine is a synthetic, direct acting catecholamine that is a β_1-receptor agonist it is available as a racemic mixture. One of the stereoisomer has a stimulatory activity. It increases cardiac rate and output with few vascular effects.
- **Therapeutic uses:** Dobutamine is used to increase cardiac output in congestive heart failure. The drug increases cardiac output with little change in heart rate, and does not significantly elevate oxygen demands of the myocardium a major advantage over other sympathomimetic drugs.

- **Adverse effects:** Dobutamine should be used with caution in atrial fibrillation, because the drug increases atrioventricular conduction. Other adverse effects are the same as those for epinephrine. Tolerance may develop on prolonged use.

6. **Phenylephrine:** Phenylephrine is α direct-acting synthetic adrenergic drug that binds primarily to α receptors and favors α_1 receptors over α_2 receptors it is not a catechol derivative and, therefore, not α substrate for COMT. Phenylephrine is a vasoconstrictor that raises both systolic and diastolic blood pressures. It has no effect on the heart itself but rather induces reflex bradycardia when given parenterally. It is often used topically on the nasal mucous membranes and in ophthalmic solutions for mydriasis. Phenyiephrine acts as a nasal decongestant, and produces prolonged vasoconstriction. The drug is used to raise blood pressure and to terminate episodes of supraventricular tachycardia (rapid heart action arising both from the atricventricular junction and atria). Large doses can cause hypertensive headache and cardiac irregularities.

7- **Methoxamine:** Methoxamine is a direct-acting, synthetic adrenergic drug that binds primarily to α receptors, with α_1 receptors favored over α_2 receptors. Methoxamine raises blood pressure by stimulating α_1 receptors in the arterioles, causing vasoconstriction this causes an increase in total peripheral resistance. Because of

its effects on the vagus nerve, methoxamine is used clinically to relieve attacks of paroxysmal supraventricular tachycardia. It is also used to overcome hypotension during surgery involving halothane anesthetics. In contrast to most other adrenergic drugs, methoxamine does not tend to trigger cardiac arrhythmias in the heart, which is sensitized by these general anesthetics. Adverse effects include hypertensive headache and vomiting.

8. **Clonidine:** Clonidine is an α_2 agonist that is used essential hypertension to lower blood pressure because of its action in the CNS. It can be used to minimize the symptoms that accompany withdrawal from opiates or benzodiazepines. Clonidine acts centrally to produce inhibition of sympathetic vasomotor centers.

9. **Metaproterenol:** Metaproterenol although chemically similar to ispoproterenol, is not catecolamine, and is resistant to methylation by COMT. It can be administered orally or by inhalation. The drug acts primarily at β_2 receptors, producing little effect on the heart. Metaproterneol produces dilation of the bronchioles and improves airway function. The drug is useful as a bronchodilator in the treatment of asthma and to reverse bronchospasm.

10. **Albuterol, pirbuterol, and terbutaline:** Albuterol, pirbuterol and terbutaline are short-acting β_2 agonists used primarily as

bronchodilators, and administered by a metered-dose inhaler. Compared with the nonselective β-adrenergic agonists, such as metaproterenol, these drugs produce equivalent bronchodilation with less cardiac stimulation.

11. **Salmeterol and formoterol:** Salmeterol and formoterol are β_2-adrenergic selective, long-acting bronchodilators. A single dose by a metered-does inhaler provides sustained bronchodilator over twelve hours compared with less than three hours for albuterol Unlike formoterol, however, salmeterol has a somewhat delayed onset of action.

II- NON-CATECHOLAMINES

1. Ephedrine:

C_6H_5—CH(OH) — CH(CH_3) — NH — CH_3

It is an alkaloid from Ephedra plants or prepared synthetically, absorbed from the G.I.T. (gastrointestinal tract) and excreted unchanged, so not affacted by monoamine oxidase (MAO) stable and so prolonged in action.

Pharmacological Actions:

Locally it is haemostatic, decongestive and mydriatic Systemically it has a sympathomimetic action stimulating, α and β receptors and stimulates the C.N.S.

Sympathomimetic action:

These are the same as adrenaline but slower in onset and more prolonged, and it is given orally.

C.N.S. actions:

It stimulates the respiratory and vasomotor centers, the cerebral cortex and reticular formation, causing insomnia.

Therapeutic uses:

a. Bronchial asthma. b. Rhinitis, 1% as nasal drops.

2. AMPHETAMINE:

$C_6H_5-CH_2-CH(CH_3)-NH_2$

It is a synthetic compound easily absorbed from G.I.T. and m. ms., partly deaminated and partly excreted unchanged in urine.

Pharmacological actions:

1- Sympathomimetic actions:-

It stimulates α and β receptors, increasing the blood pressure, relaxing the G.I.T. and urinary bladder and locally mydriatic.

2- C.N.S actions:

It stimulates the cerebral cortex and reticular formation, the vital medullary centers and the spinal cord, increasing mental and physical activities and anorexigenic. It is used illegally in race horses.

Therapeutic uses:

a. Mental and physical fatigue. b. Psychic depression.

c. Obesity.

3- Tyramine:

$-CH_2-CH_2-NH_2$

HO

It acts by releasing noradrenaline from its stores. It also inhibits M.A.O. enzyme.

Table (8): Summary of adrenergic agonists

CATECHOLAMINES
- Rapid onset of action
- Brief duration of action
- Not administered orally
- Do not penetrate the blood-brain barrier

Drug	Receptor specificity	Therapeutic uses
Epinephrine	α_1, α_2 β_1, β_2	Acute asthma Treatment of open-angle glaucoma Anaphylactic shock In local anesthetics to increase duration of action
Norepinephrine	α_1, α_2 β_1	Treatment of shock
Isoproterenol	β_1, β_2	As a cardiac stimulant
Dopamine	Dopaminergic α_1, β_1	Treatment of shock Treatment of congestive heart failure Raise blood pressure
Dobutamine	β_1	Treatment of congestive heart failure

NONCATECHOLAMINES
Compared to catecholamines:
- Longer duration of action
- All can be administered orally

Drug	Receptor specificity	Therapeutic uses
Phenylephrine	α_1	As a nasal decongestant Raise blood pressure Treatment of paroxysmal supraventricular tachycardia
Methoxamine	α_1	Treatment of supraventricular tachycardia
Clonidine	α_2	Treatment of hypertension
Metaproterenol	$\beta_2 > \beta_1$	Treatment of bronchospasm and asthma
Terbutaline *Albuterol*	β_2	Treatment of bronchospasm (short acting)
Salmeterol *Formoterol*	β_2	Treatment of bronchospasm (long acting)
Amphetamine	α, β, CNS	As a CNS stimulant in treatment of children with attention deficit syndrome, narcolepsy, and appetite control
Ephedrine	α, β, CNS	Treatment of asthma As a nasal decongestant Raise blood pressure

SYMPATHOLYTICS

(Adrenolytics, Adreno-ceptors blocking agents)

Definition: these are drugs which inhibit the responses of the effector cells to administered adrenergic drugs and to sympathetic nerve stimulation.

Classifications of the adrenergic blockers:

Adrenoceptors blocking agents are classified according to site of action into:

1. Alpha-adrenergic blocking agents:

These prevent the vasoconstriction and other excitatory effects on smooth muscles produced by catecholamines. They compete with sympathetic transmitter for the receptors in the effector cells.

2. Beta-adrenergic blocking agents:-

These drugs block the cardiac, bronchial dilator and metabolic actions of catecholamines.

3. Antiadrenergics or adrenergic neurone blocking agents:-

a) Drugs interfering with the synthesis as alphamethyldopa.

b) Drugs depleting the stores of catecholamines as reserpine.

c) Drugs inhibiting the transmitter release as guanithidine.

1- Alpha adrenergic blocking agents:

These are classified according to their chemical nature into:-

1) Ergot alkaloids.
2) Beta - haloalkyl amines as phenoxybenzamine.
3) Imidazoline as tolazoline (priscol) and regitine (phentolamine).

4) Dipenzapine derivatives as ilidar (azapetine).

5) Benzodioxans e.g. piperoxane.

6) Yohimbine.

1) Ergot alkaloids

Ergot is a fungus which grows parasitically on the grains of rye and other cereals. The alkaloids of ergot are ergotoxine, ergotamine and ergometrine. Erotoxine and ergotamine are alpha blocking agents prevent the effector cells from responding, to stimulation of adrenergic nerves or injection of adrenaline or noradrenaline. Ergometerine shows little or no alpha adrenergic blocking activity, but it has a stimulant effect on the uterine muscles.

Pharmacological action:

1-Ergotoxine and ergotamine have an alpha blocking activity, but they have a direct peripheral vasoconstrictor effect.

2- They decrease the heart rate by:

- Central vagal stimulation.
- Direct depression of the cardiac muscles.
- Reflex stimulation of the baroceptors of the carotid sinus.

3- Ergotamine stimulate the heart regulating centre and inhibit the medullary centres except the vagal and the chemoreceptor trigger zone are stimulated.

Therapeutic uses:

1- Dihydroergotamine: with caffeine are used for the treatment of migrane.

2- Ergometrine maleate (methergine) is used for treatment and prevention of post partum hoemorrhage and help the involution of the uterus. (0.2 mg orally or i.m.).

2) **Beta-haloalkyl amines:**

Phenoxybenzamine

It is a very powerful and highly specific alpha adrenolytic action.

Pharmacological actions:

It causes a marked fall in elevated blood pressure with increased cardiac output in man, which may be attributed to blocking of the adrenoceptors and in part to nor adrenaline release and inhibition of its uptake.

Therapeutic uses:-

1. Hypertension. 2. During chloroform anaesthesia to prevent cardiac arrhythmia.

3) Imindazolines as:- Tolazolin and regitine

They are competitive alpha—blockers and fall in blood pressure. They are used therapeutically in peripheral vascular diseases and hypertension.

4) Dibezapine: Ilidor (azapetine)

It causes a fall in blood pressure and increases the peripheral blood flow.

5) **Benzodioxane: <u>Piperoxane</u>**

It is not widely used therapeutically because it has many undesirable reactions.

6- <u>Yohimbine</u>

It is an alkaloid from the tree yohimbine. It has a competitive adrenolytic action, antidiuretic action due to the release of antidiuretic hormone.

<u>2- Beta adrenergic blocking agents</u>:

1) Dichloroisoprenaline.
2) Pronethoiol.
3) Propranolol blocks β_1 and β_2
4) Oxprenolol blocks β_1 and B_2.
5) Practolol β_1 - specific blocker.
6) Atenolol β_1 - specific blocker.
7) Butoxamine β_2 - specific blocker.

They block the beta-effects of adrenaline. They produce decrease in blood pressure due to peripheral vosodilatation. They are used therapeutically for the treatment of angina, hypertension and peripheral vascular diseases.

<u>3- Antiadrenergics:</u>

These are the drugs which inhibit either the synthesis or storage or release of noradrenaline.

a) **Drugs inhibiting the synthesis of nora rendine:**

e.g. alpha methyl dopa (aldomet); it inhibits the decarboxylation of dopa into dopamine and finally noradrer line.

b) **Drugs inhibiting the storage of noradrerlriline:**

e.g. reserpine. It is an alkaloid from Rawolfia. It inhibits the binding of noradrenaline with ATP in the granules and consequently inhibit the storage of noradrenaline.

c) **Drugs inhibiting the release of nor adrenaline:**

e.g. Guanethidine and bretylium. They prevent the release of nor adrenaline from the sympathetic nerve fibres.

The antiadrenergics are used therapeutically for the treatment of hypertension.

B. CHOLINERGIC DRUGS

1- DRUGS ACTING ON PERIPHERAL CHOLINERGIC RECEPTORS

These drugs affect all plain muscles, heart muscle and exocrine glands. They are either stimulants (parasympathomimetics) or depressants (parasympatholytics).

PARASYMPATHOMIMETICS

(CHOLINIMIMETICS)

Definition:

These are the drugs which stimulate the peripheral cholinergic receptors in plain muscles, heart muscle and exocrine glands.

Classification:

A. Choline esters:

1. Acetylcholine.
2. Methacholine.
3. Carbachol.
4. Bethanechol.
5. Furtrethonium.

B. Naturally occurring choline alkaloids:

1. Muscarine.
2. Pilocarpine.
3. Arecoline.

C. Inhibitors of cholinesterase:

1. Physostigmine.
2. Neostigmine
3. Organic phosphorous esters.

A. Choline esters

1. Acetylcholine

$$CH_3-\overset{O}{\overset{\|}{C}}-O-CH_2-CH_2-\overset{CH_3}{\overset{|}{\underset{CH_3}{\underset{|}{N}}}}-CH_3$$

Acetylcholine is a quaternary ammonium base. The estrification of choline to produce acetylcholine is helped by the enzyme choline acetylase.

It is available for medical use in the form of its chloride or bromide salts which are readily soluble in water.

Absorption and fate:

Acetylcholine is inactive orally owing to its rapid inactivation in the gastrointestinal tract.

It is given by injection and rapidly inactivated in the body by the true and the pseudocholinesterase. The former is present in the nervous and cholinergic structures and in the blood cells, while the latter is present in the blood plasma. Acetylcholine is distributed extracellularly.

Pharmacological actions:

Acetylcholine possesses two main types of actions:

1. Muscarine-like or parasympatomimetic action, which consists of direct stimulation of all peripheral cholinergic receptors and is blocked by atropine (see table).
2. Nicotine-like action, which consists of the stimulation of the central cholinergic receptors in the autonomic ganglia, adrenal medulla and in the skeletal muscles. Nicotinic action of acetylcholine is blocked on skeletal muscle by skeletal muscle relaxants and on the ganglia by ganglionic blockers.

Preparations:

It is available as chloride or bromide salts. It is present in ampoules as crystaline powder.

Therapeutic uses:

Acetylcholine is unsuitable as therapeutic agent because of its instability and transient actions. But, it may be used in auricular tachycardia and hypertension.

2. Methacholine

It is a synthetic ester i.e. acetyl-B-methyl choline. It is available as the chloride or bromide salts. It is soluble in water and alcohol.

Absorption and fate:

It is effective after oral administration but it is better to be given by injection. It is not destroyed by the pseudocholinesterase enzyme. So, the duration of action is longer.

Pharmacological actions:

1. Methacholine possesses mainly muscarinic actions and lacks the nicotinic actions of acetylcholine. The actions last in about half an hour
2. The drug produces peripheral vasodilatation and fall in blood pressure which compensated by tachcyardia and recovery of the pressure.
3. Other actions are increased salivary, lacrimal and sweat secretions.

Therapeutic uses:

1. Auricular tachycardia.
2. Peripheral vascular disorders.
3. Diagnostic test for atropine poisoning.

3. Carbachol

Carbachol is the carbamic ester of choline. It is available as chloride salts which is soluble in water.

Absorption: Carbachol is readily absorbed from the alimentary tract. It is highly resistant to the cholinesterase.

Pharmacological actions:

1. Carbachol is a powerful cholinergic drug with prolonged action.
2. It has both muscarinic and nicotinic actions but more pronounced on the alimentary tract and the urinary bladder.

Therapeutic uses:

1. For the treatment of constipation.
2. For the treatment of ruminal stasis in cattle (1-2 mg, s/c, repeated).
3. In case of urine retention.

4. Bethanechol.

5. Furtrethonium.

Pharmacological actions:

1. Both have powerful muscarinic actions, mainly on the alimentary tract and urinary bladder as carbachol.
2. Nicotinic actions are appeared at a higher dose level than muscarinic actions.
3. Bethanechol is not hydrolysed by cholinesterase and has a prolonged and weak action.

Therapeutic uses:

1. Post-operative retention.
2. Paralytic ileus.

B. Naturally occurring alkaloids

1. Muscarine

HO, CH_3, O, $-CH_2-\overset{+}{N}(CH_3)_3$

Muscarine

It is an alkaloid isolated from mushrooms. It is related chemically to choline. It produces only direct stimulation of all cholinergic receptors. It has not therapeutic uses.

2. Pilocarpine

C_2H_5, $-CH_2-$, $N-CH_3$, O, O, N

Pilocarpine

Pilocarpine is the natural alkaloid of pilocarpus jaborandi leaves. It is available as nitrate which is soluble in water.

Absorption and fate:

It is readily absorbed from the gut. It is inactivated in the liver and the metabolic products are excreted in urine.

Pharmacological actions:

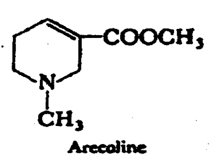
1. Pilocarpine has only muscarinic and not nicotinic action.

2. It acts mainly on gland secretion specially salivary and sweat glands as well as on eye producing miosis and spasm of the ciliary muscle. So it is strong diaphoretic.

Therapeutic uses:

1. In case of glaucoma to reduce intraocular tension and alternatively to physostigmine.
2. For the treatment of atropine poisoning.
3. For the promotion of hair growth in the form of hair lotion.

2. Arecoline



Arecoline

It is the natural alkaloid obtained from the seeds of areca nut and is available as hydrochloride.

Pharmacological actions:

1. Arecoline has both muscarinic and riicotinic actions.
2. Its secretion and motility stimulating powers have been used for purgative effect in horse.

Therapeuticuses:

1. For the treatment Echinococc :s granulosus infestations in dogs.
2. For the treatment of constipation in horse.

C. Inhibitors of cholinesterase

Mode of action of anticholinesterases:

It is claimed that acetylcholinesterase possesses an active site which reacts directly with the substrate. This active site contains two sub-sites, an anionic site which is chiefly concerned with the hydrolytic process. The anionic site is negatively charged and reacts with positively charged cations.

Hydrolysis of acetylcholine can be inhibited by substances which combine with the active site of cholinesterase. These substances are of 2 types:-

1. Reversible inhibitors such as physostigmine and neostigmine.
2. Irreversible inhibitors such as the organic phosphorous compounds.

Physostigmine (Eserine)

CH_3
CH_3NHCOO
N N
CH_3 CH_3

Physostigmine is an alkaloid obtained from the dried seeds of calabar beans and is available as physostigmine salicylate which is easily soluble in water.

Mode of action: It inhibits cholinesterase enzyme, thus prolongs both the muscarinic and nicotinic actions of acetylcholine. It inactivates cholinesterase in a reversible manner.

Pharmacological actions:

1. The muscarinine actions of eserine are more pronounced on the plain muscles of GIT and urinary tracts, and also produce bradycardia and peripheral vasodilatation.
2. Eserine produces miosis and accommodation of the eye for the near objects, reduction in the intraocular tension.
3. Eserine stimulates contraction of the skeletal muscles due to the nicotinic action of the drug and the direct action on the skeletal muscles.
4. Eserine stimulates the central nervous system but in large dose which followed by depression and death.

Therapeutic uses:

1. Glaucoma
2. For breaking down the adhesions between the iris and cornea or lens alternatively with atropine.
3. Myasthenia gravis in man.

Prostigmine (Neostigmine)

$(CH_3)_2NCOO-C_6H_4-N^+(CH_3)_3$

Prostigmine is a synthetic compound. It is available as methylsulfate and bromide. The former is given parenterally and the later is given orally.

Mode of action:

Prostigmine is an anticholinesterase drug as physostigmine.

Pharrnacoloigical actions:

1. It has both muscarinic and nicotinic actions of acetycholine but it is less potent than eserine on the cardiovascular system, exocrine secretions and ocular muscles.
2. It stimulates the GIT and urinary tract.
3. It has a direct stimulant action on the skeletal muscles and a mild central depressant action.

Therapeutic uses:

1. For the diagnosis and treatment of myasthenia gravis.
2. Atony of the urinary bladder.
3. Antidote in curare toxicity.
4. Antidote in ganglion blockers toxicity.
5. Glaucoma.
6. Diagnosis of early pregnancy in women.

Doses: Horses and cow: 4 - 25 mg, dog and cat, 0.025 mg/kg.

Organic phosphorous compounds

These are irreversible inhibitors of the cholinesterase activity. Thus, they produce very powerful and prolonged muscarinic and

nicotinic actions. Organic phosphorous compounds are commonly used now as insecticides; among these compounds are malathion, parathion, asuntol and neguvon.

Mode of action:

Irreversible inhibitors of cholinesterase.

Pharmacological actions:

1. The compounds produce powerful muscarinic and nicotinic actions.
2. They produce stimulation of the central nervous system.

Toxicity:

The toxic effect can be attributed to the cholinomimetic, skeletal muscle and C.N.S effects.

Treatment of poisoning (toxicity):

1. Intravenous injection of atropine (100 μg / kg in dog, 60 μg / kg in ruminants).
2. Administration of cholinesterase reactivator e.g. oximes.

The organophosphates inactivate cholinesterase by phosphorylating the active centre of the enzyme. The oximes dephosphorylate the enzyme. Among oximes are pralidoxime chloride (2-pam) and obidoxime chloride.

3. Artificial respiration if necessary.

PARASYMPATHOLYTICS

(CHOLINOLYTICS)

Definition:

These are the drugs which compete with acetylcholine at the muscarinic (peripheral) cholinergic receptors but not the central receptors.

The chief members of this group are classified according to their nature into:

1. The naturally occurring alkaloids (atropine, hyoscine and hyoscyamine).
2. The synthetic esters as homatropine, and eucatropine.

1. Naturally occurring alkaloids

1. Atropine

CH_2—CH—CH_2 CH_2OH
NCH$_3$ CH—O—CO—C—(phenyl)
CH_2—CH—CH_2 H

Atropine is obtained from the belladonna plants i.e. *Atropa belladonna* and *Datura stramonium.*

Absorption and fate:

Atropine is absorbed from GIT and injection sites. It is inactivated in the liver by hydrolytic enzyme. It and its metabolic products excreted by the kidneys.

Mode of action:

Atropine competes with acetylcholine for the peripheral cholinergic receptor sites in the effector cells i.e. competitive antagonism.

Pharmacological action:

1. Atropine in therapeutic doses inhibits all the muscarinic actions of acetylcholine, but in toxic doses, it may also the nicotinic action. Inhibition of the muscarinic actions of acetylcholine produces effects similar to those produced by stimulation of the sympathetic receptors.

2. In therapeutic dose, atropine produces mild stimulation of the vagal center as well as mild stimulant effect on respiratory centre. In large doses, atropine has a stimulant excitatory action resulting in restlessness, excitation and irritability. With toxic doses, the central stimulant effect is followed by depression and death may occur due to paralysis of the respiratory centre.

Therapeutic uses:

1. For eye examination.
2. For prevention of adhesions in case of iritis.
3. Bronchial asthma.
4. Intestinal colic.
5. Renal and biliary colic.
6. Treatment of peptic ulcer.
7. Bradycardia associated with abnormal carotid sinus reflex in man.

8. Toxicity of cholinomimetic drugs.

9. Pre-anaesthetic medication:

   a) To suppress excessive secretions of the respiratory tract.

   b) To prevent reflex vagal inhibition of the heart.

   c) To counteract the depressant effect of the anesthetic on the respiratory centre.

Toxicity:

The symptoms of toxicity include dryness of the mouth, dilatation of the eye pupil, tachycardia muscular inccordination and sometimes respiratory failure.

Treatment of toxicity:

1. Perform the gastric lavage.
2. Administer the antidote e.g. pilocarpine or methacholine at intervals till the mouth becomes moist.
3. The mental symptoms can be controlled by a barbiturate.
4. Perform artificial respiration.

Dosage:

Dog: 30 -100 µg / kg; Ruminants: 30 - 60 µg / kg

In ophthalmology, 1 % atropine solution is used.

2. Scopolamine (hyoscine)

```
 ,CH---CH----CH2          CH2OH
/      |     |            |
O      NCH3  CH—O—CO—C———[C6H5]
\      |     |            |
 CH---CH----CH2           H
```

it is an alkaloid obtained from the flower of *Hyoscyamus nigra*; it differs from atropine in that it is a central depressant and has more powerful effect on the eye and exocrine glands. It has less effect on the heart.

3. Hyoscyamine

It is an alkaloid obtained from *Datura stramonium* and *Atropa belladonna*. It has the same action of atropine and more antisposmodic action. It is used with drastic purgatives to counteract gripping.

2. Synthetic atropine substitutes

Many semisynthetic or synthetic analogues have been developed in attempts to find a mydriatic with a short duration of action and a spasmolytic whose action is free of side effects.

Homatropine hydrobromide and eucatropine hydrochloride are used for the examination of the eye and their effect lasts for about 12 hours to two days.

Methscopolamine bromide: which is devoid of the central effects of hyoscine and is used in the treatment of peptic ulcer, renal colic and cystitis.

2. DRUGS ACTING ON CENTRAL CHOLINERGIC RECEPTORS

a) Drugs acting on the autonomic ganglia

1. Ganglionic stimulants:-

These are drugs which stimulate the central cholinergic receptors in the autonomic ganglia as:

1. **Acetylcholine:** It acts as ganglionic stimulant in small dose.
2. **Nicotine:** It is an alkaloid obtained from Tobacco leaves.

Pharmacological actions:

1. In small doses, it has a stimulant action on the central cholinergic receptors as autonomic ganglia, skeletal muscles and adrenal medulla, larger doses produce blockage of these receptors. The initial stimulation is due to a depolarizing action but depression is due to persistent depolarization.
2. Initial stimulation followed by depression of the central nervous system.
3. Increased motility of G.I.T. and gastric secretion.
4. Vasoconstriction, tachycardia and increased cardiac output with increased blood pressure.

3. **Lobeline:** It is an alkaloid from *Lobelia inflata* leaves. It has a similar but less potent than nicotine. It is mainly used as respiratory stimulant.

2. Ganglionic blockers:-

These are the drugs which block the transmission of nerve impulses across the autonomic ganglia. They are classified according to their mode of action into:-

A) Depolarizing ganglionic blockers:

As large doses of acetylcholine, nicotine and lobeline. They produce initial stimulation followed by blocking. They produce its actions by persistent depolarization of the postganglionic membrane.

B) Competitive ganglionic blockers:

They compete with acetylcholine for the same central cholinergic receptors in autonomic ganglia as tetraethyiammonium, penta- and hexamethonium. They are used therapeutically in hypertension) peripheral vascular diseases and acute pulmonary oedema.

b) Drugs acting on the skeletal muscles

Drugs acting on the skeletal muscles are classified according to their action into:-

1. Skeletal muscle stimulants.
2. Skeletal muscle relaxants.

1. Skeletal muscle stimulants: such as small dose of acetylcholine, nicotine and lobeline. Methacholine and anticholinestrase drugs are also examples.

2. Skeletal muscle relaxants: Skeletal muscle relaxants are grouped according to their site of action into:

A) Peripheral: They act either presynaptically or postsynaptically at the neuromuscular junction.

a) **Presynaptic:** These include drugs which inhibit the synthesis of acetylcholine (such as hemicholinium) or release of acetylcholine (such as botulinum toxin).

b) **Postsynaptic**: (skeletal muscle blockers): They are classified according to their mechanism of action into:

1. **Competitive muscle blockers**: They act by competition with the acetylcholine at the central cholinoceptors of the neuromuscular junction. They include tubocurarine (curare) and gallamine (flexidil).

2. **Depolarizing muscle blockers:**

They act by producing depolarization leading to muscular tremors at first followed by muscular paralysis. They include succinylcholine, suxamethonium and decamethonium.

B) Central:

They act centrally either by depressing motor output from the cerebral cortex and spinal cord (as central nervous system depressants) or by inhibiting the transmission of interneurons of spinal cord (as mephensin and meprobamate).

III. DRUGS ACTING ON THE CENTRAL NERVOUS SYSTEM

- Physiological background
- Cerebral stimulants
- Medullary stimulants
- Spinal cord stimulants
- Sedatives and hypnotics
- Anticonvulsants
- Tranquilizers
- Analgesics
- Anesthetics

BY: ABUBAKR M. EL-MAHMOUDY, PhD

PHYSIOLOGICAL BACKGROUND

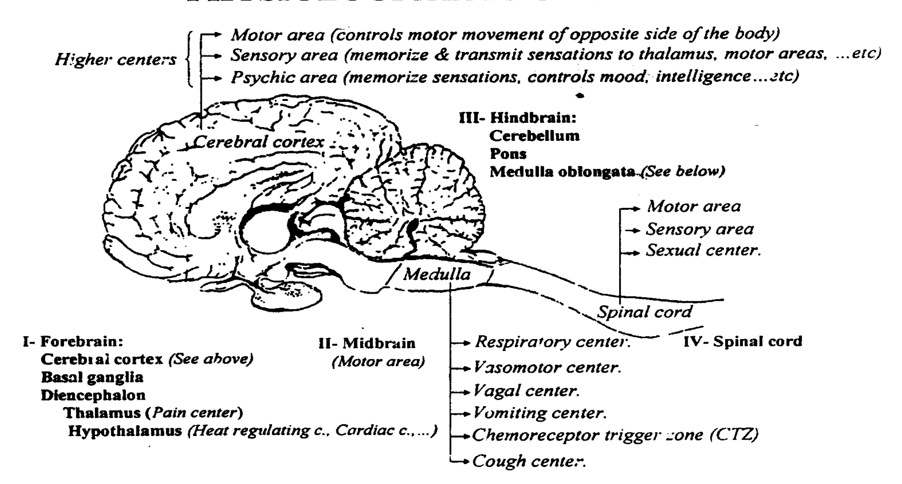


Fig. 21: Schematic representation of CNS structure. *Italic parts are those of pharmacologic interest.*

Anatomically, the central nervous system consists of 4 main parts:

1- Forebrain
2- Midbrain
3- Hindbrain
4- Spinal cord

1. Forebrain:

It includes cerebral hemispheres and diencephalon.

a. Cerebral hemispheres: it includes cerebral cortex and basal ganglia. **The cerebral cortex** includes the higher centers which control consciousness, intelligence and memory. The cortex is divided into 4 areas, namely, motor, premotor, sensory and psychic areas. The motor and premotor areas are responsible for controlling motor movements of the other side of each hemisphere. The sensory area is responsible for controlling all sensations of the other side of each hemisphere. The Psychic area is related to the corresponding sensory area and responsible for storing a memory of all sensations. The psychic area is therefore, responsible for the mood and temperament of the subject.

The basal ganglia lie at the base of each hemisphere, they are responsible for controlling autonomic reflexes for maintenance of posture.

b. Diencephalon: it includes the thalamus and hypothalamus. **The thalamus** is a relay station that receives impulses of superficial, deep, visceral and special sensations; it contains pain center. **The hypothalamus** contains cardiac, osmotic, heat regulating and sleep centers.

2. Midbrain: It connects between fore and hind brains. It contains motor area that is stimulated by analeptic drugs leading to clonic convulsions if given in large doses.

3. The hind brain:

It includes the cerebellum, the pons and the medulla oblongata.

a. The cerebellum: It controls the adjustment of different postures and coordination of fine movements.

b. The pons and the medulla oblongata: They contain most of the cranial nerve centers. The dorsum of the medulla contains the vital centers, namely, respiratory and vasomotor centers, in addition to vagal, vomiting and cough centers besides the chemoreceptor trigger zone (CTZ) which is a relay station before the vomiting center.

4. Spinal cord:

It is often thought that the spinal cord is only a conduit for signals from the periphery of the body to the brain, or in the opposite direction from the brain back to the body. This is far from the truth. Even after the spinal cord has been cut in the high neck region, many highly organized spinal cord functions still occur. For instance, neuronal circuits in the cord can cause (1) walking movements, (2) reflexes that withdraw portions of the body from painful objects, (3) reflexes that stiffen the legs to support the body against gravity, and (4) reflexes that control local blood vessels, gastrointestinal movements, or urinary excretion. In addition, sexual centers are present in the spinal cord controlling the sexual activity.

The basic structural and functional unit in CNS is the nerve cell, or neuron. The neuron has three parts, a cell body, a dendritic tree and an axon. The CNS consists of about 100 billions of neurons, many of which are linked to form diffuse functional networks. All sensations and motor orders are transmitted from one neuron to the next via specialized structures called synapses. Synapses are thus junctional points and therefore are sites of focus for control of signal or impulse transmission within CNS. Transmission of impulses is mediated via release of chemical substances known as neurotransmitters. A neurotransmitter is synthesized and released from one neuron (presynaptic neuron) to the synaptic cleft where it combines with a specific receptor located on the surface of the next neuron (postsynaptic neuron) producing and excitatory or inhibitory effect. (Fig. 22)

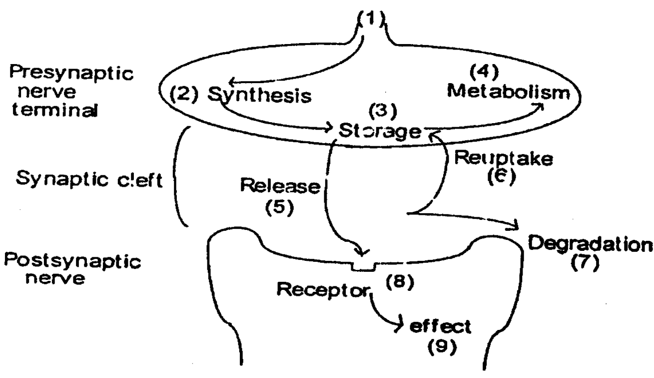


Fig. 22: Simplified schematic of steps in interneuron transmission of a nerve impulse. (1) Action potential propagated in the presynaptic nerve, (2) transmitter synthesis, (3) transmitter storage, (4) interneuron transmitter breakdown or inactivation, (5) transmitter release into the synaptic cleft, (6) transmitter reuptake into presynaptic terminal, (7) transmitter synaptic degradation, (8) transmitter attachment to postsynaptic receptor, and (9) receptor-induced increase or decrease in ionic conductance or altered cellular process. *(From Veterinary Pharmacology and Therapeutics. H. R. Adams. 8th Ed.)*

Drugs acting on different parts of CNS mostly act through modulation of one of the neurotransmitters located there. Some drugs, however, are non-specific in their actions. These transmitters are grouped to 4 groups according to their nature and the roles they play within CNS (Fig. 23).

The 1st group includes transmitters used in fast point-to-point neural circuits which are amino acids (left in the figure) in addition to a few cholinergic synapses with N receptors. Glutamate is the main excitatory transmitter. It depolarizes neurons by triggering an increase in membrane Na^+ conductance. γ–Amino butyric acid (GABA) is the main inhibitory transmitter. It hyperpolarizes neurons by increasing their membrane Cl^- conductance and stabilizes the resting membrane potential. Glycine is also inhibitory transmitter mainly in the spinal cord.

In addition to fast point-to-point signaling, the brain processes are more diffuse and regulatory systems which use monoamines (2nd group) as their transmitters (bottom right in Fig. 23). CNS disorders as Parkinson's disease, depression, migraine and schizophrenia are associated with disturbances in monoamine transmitters.

Many peptides (3rd group; top right) are found within central neurons and involved in the regulatory processes within CNS together with monoamines.

The 4th group is recently added which involves nitric oxide (NO) as a transmitter in the brain. Information about individual most important transmitters is listed below:

AMINO ACIDS

γ-Aminobutyric acid (GABA):

It rapidly inhibits CNS via its action on $GABA_A$ and $GABA_B$ receptors in the brain. $GABA_A$ receptors are postsynaptic and blocked by the convulsant drug bicuculline. $GABA_B$ receptors are present both pre-and postsynaptically but mostly presynaptic. They are not blocked by bicuculline but are selectively activated by baclofen. Activation of $GABA_B$ receptors results in a reduction in transmitter release (mainly glutamate) therefore used for controlling muscular spasms. Drugs which act through modification of GABAergic synaptic transmission include benzodiazepines, barbiturates, and valporate.

Glycine:

It is the inhibitory transmitter in spinal interneurones via yet-undetermined receptor which is antagonized by strychnine. The release of glycine is prevented by tetanus toxin. Both substances (strychnine and tetanus toxin) cause convulsions.

Glutamate:

It excites all central neurons via kainate and AMPA (a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and NMDA (N-methyl-D-aspertate) receptors. A related amino acid that having nearly the same action of glutamate via the same receptors especially NMDA ones is aspertate. Lamotrigine is an antiepileptic drug which acts via inhibiting presynaptic glutamate release.

MONOAMINES

Acetylcholine

It is widely distributed throughout CNS. It is mainly excitatory via activation of muscarinic receptors (M_1~M_5). Some fast point-to-point transmissions, however, are done via nicotinic receptors (N_1 and N_2).

Cholinergic neurons are involved in cortical arousal responses and in memory. Atropine and atropine like drugs may impair memory (amnesia). The amnesic action of hyoscine is clinically used in anesthetic pre-medication. They are also used for their central actions in motion sickness and Parkinson's disease. Loss of cholinergic neurons and memory are prominent features of Alzheimer's disease which has no complete treatment till now; however a modest improvement is observed in 50% of patients upon administration of anticholinesterases as rivastigmine.

Dopamine

It is a major transmitter and generally inhibits CNS via activation of dopamine receptors (D_1 ~ D_5). The dopaminergic pathways are involved in the following regulations:

- Control of voluntary fine movements and thus its degeneration results in Parkinson's disease, while dopamine agonists (*l*-dopa) are beneficial in its treatment.
- Control of prolactin release, and thus dopamine antagonists (bromocriptine = lactodel®) are used to stop milk production when necessary.

- Control of CTZ which contains dopamine receptors and thus dopamine antagonists (metoclopramide = primperan®) are useful anti-emetics.
- Stability of mood and psychic condition, where over activity of certain pathways in CNS leads to schizophrenia.

Adrenaline & Noradrenaline

They excite and inhibit central neurons via activating α and β receptors. They seem to be involved in the control of sleep where they are responsible for wakefulness via activating α adrenoceptors especially α_2 subtype. They are also involved in blood pressure regulation. Impairment of noradrenergic function may be associated with depression.

It should be mentioned that circulating noradrenaline can not pass the blood brain barrier and CNS has its own transmitter.

Serotonin (5-HT):

5-HT is involved in the control of sleep, wakefulness, pain, emotions, temperature and appetite as well as release of other CNS transmitters via its action on 5-HT receptor family which are numerous ($5\text{-}HT_1 \sim 5\text{-}HT_7$). Important examples are:

- Like noradrenaline, impairment of certain 5-HT pathways leads to depression.
- Some 5-HT receptors occur in CTZ and its antagonists have anti-emetic effects.
- Some 5-HT receptors occur in cranial blood vessels and the agonist sumatriptan relieves migraine by constricting blood vessels that were dilated during the migraine attack.

- 5-HT is involved in the control of sensory transmission and 5-HT agonists as LSD (lysergic acid) cause hallucinations.

Histamine

It is relatively minor transmitter within CNS and involved in the control of arousal, temperature, and vascular dynamics via its action on histamine receptors (H_1 ~ H_4). Importantly, H_1 antagonists cause sedation and have anti-emetic actions.

NEUROPEPTIDE TRANSMITTERS

They include:

- **Substance P** which act via activation of NK_1 receptor mainly.
- **Opioid peptides** (endorphins = endogenous morphines) as β- endorphin, Met-enkephalin, Leu-enkephalin and dynorphin. They are widely distributed in CNS and involved in producing analgesia via their actions on opiate receptors (μ = mu, δ = delta, and κ = kappa).

Substance P and opioid peptides are involved in pain pathways.

NITRIC OXIDE

It differs from all other neurotransmitters in being a gas and thus not stored in vesicles; its synthesis (by the action of NOS = nitric oxide synthase on the precursor amino acid *l*-arginine) and action are immediate. It is present in the brain and associated with long term memory and modulates release of other transmitters.

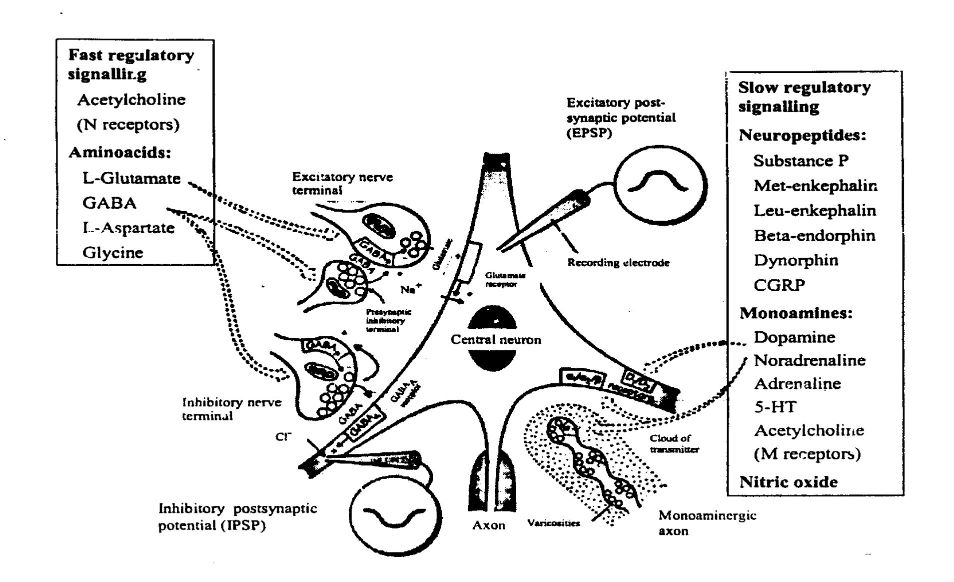


Fig. 23: Transmitters within central nervous system. *Modified after M. J. Neal, Medical Pharmacology at a Glance, 4th Ed.*

DRUGS ACTING ON CNS

Drugs acting on CNS may be divided according to their actions into:

1. CNS STIMULANTS

which are further classified according to their site of action into:

- Cerebral stimulants
- Medullary stimulants
- Spinal cord stimulants

2. CNS DEPRESSANTS

which are further classified according to their degree of CNS depression into:

- Sedatives
- Hypnotics
- Anticonvulsants
- Tranquilizers
- Analgesics
- Anesthetics

1. CNS STIMULANTS

1.1. Cerebral stimulants

Def.: these are the drugs which stimulate cerebral cortex and higher centers of the brain. They produce wakefulness & ↑ mental activity.

Members:

- Xanthine alkaloids
- Amphetamine
- Nicotine
- LSD (Lysergic acid)
- Ritalin (methylphenidate)
- Atropine
- Cocaine

1.1.1. Xanthines

Def.: They are methylated xanthines and include caffeine, theobromine & theophylline. These alkaloids are occurring naturally in tea, coffee, cocoa & cola.

Actions:

CNS:

- They produce descending stimulation of sensory areas in CNS producing wakefulness, refreshment, increased mental activity which may be accompanied by tremors in some individuals.
- As CNS stimulants, the alkaloids are ordered as follows: Caffeine > Theophylline > Theobromine
- They stimulate respiratory, vasomotor and vagal centers.
- Large doses of xanthines produce descending stimulation of motor areas of CNS producing excitement and convulsions.

Mechanism of action of xanthines as CNS stimulants:

Xanthines inhibit phosphodiestrase enzyme, which is responsible for conversion of active 3,5 cyclic AMP into 5 AMP (inactive). The active form is responsible for phosphorylation processes and activation of nerve cells (Fig. 24).

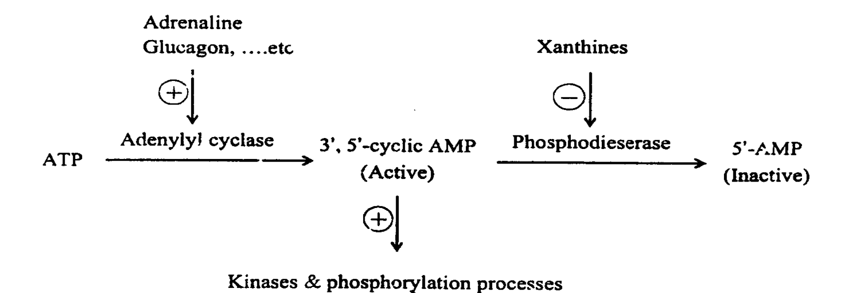


Fig. 24: Mechanism of action of xanthines

CVS:

- As cardiovascular drugs, xanthine alkaloids are ordered as follows: Theophylline > Theobromine > Caffeine.
- CVS is affected centerally and peripherally as follows:

1. Central actions:

- Stimulation of vagal center, producing bradycardia with tendency to lowering blood pressure.
- Stimulation of vasomotor center producing vasoconstriction with tendency to increasing blood pressure.

2. Peripheral actions:

- Direct myocardial stimulation; this effect antagonizes the bradycardia caused by the central vagal stimulation; so the net action may be bradycardia, tachycardia or no change in cardiac rhythm. At large doses, the direct myocardial stimulation predominates and a definite tachycardia occurs.
- Direct vasorelaxant effect on peripheral blood vessels; this effect antagonizes the vasoconstriction caused by the central stimulation of vasomotor center.
    - The net results of all the above effect is slight rise in blood pressure at therapeutic doses.

US:

- Xanthines have diuretic effect via:
    - ↑ renal blood flow,
    - ↑ permeability of glomerular epithelium,
    - ↓ tubular reabsorption of H_2O and ↑ chloride secretion,
    - ↓ ADH release.

- As diuretics, xanthine alkaloids are ordered as follows: Theophylline > Theobromine > Caffeine

RS:

- Theophylline, particularly, as well as its derivatives like aminophyiline have direct bronchial smooth muscle relaxant effect.

DS:

- Xanthines increase gastric acid secretion and potentiate action of histamine.
- They relax biliary smooth muscle.
- Large dose of xanthines especially theophylline have local irritant effect that leads to nausea and may be vomition.

Skeletal muscles:

Caffeine, particularly, has anti-fatigue and muscle better-performing actions via central motor action and peripheral releasing of intra-sarcoplasmic Ca^{++} increasing intracellular calcium.

Indications:

- Narcotic and barbiturate poisonings
- Fatigue, headache and influenza together with aspirin
- Cardiac edema (congestive heart failure)
- Bronchial asthma and biliary coloic.
- Migraine headache together with ergotamine (Cefergot)

Contraindications:

- Peptic ulcer. - Hypertension. - Gout.

Table 9: Relative pharmacological actions of xanthine alkaloids on different body effectors.

	CNS	Cardiac stimulation	Vaso-dilatation	Smooth muscle relaxation	Diuresis
Caffeine	+++	+	+	+	+
Theophylline	++	+++	+++	+++	+++
Theobromine	+	++	++	++	++

1.1.2. Amphetamine

Def: It is a sympathomimetic drug has, in addition, the following actions on CNS.

Actions:

- Stimulation of cerebral cortex and reticular formation by facilitation of excitatory transmitters.
- Small dose causes alertness & wakefulness increasing mental activity and physical performance followed by depression and fatigue. Moderate dose causes anxiety & tremors; while larger doses cause schizophrenia-like syndrome (paranoid).
- Anorexia by stimulation of satiety center.

Uses:

- Mental and physical fatigue.
- Psychic depression.
- Obesity.

1.1.3. Ritalin

As amphetamine but weaker in action and thus it is less toxic.

1.1.4. Atropine

It is a sympatholytic drug via blocking of M receptors having, in addition, the following central actions:

- Sensory stimulation in the form of restlessness, irritability disorientation and hallucinations.
- Stimulates respiratory and vagal centers (but vagal stimulation is antagonized by peripheral blocking of cardiac M receptors).
- Inhibits vomiting center.
- It has anti-Parkinsonian action as extra acetylcholine contributes in the tremors and rigidity associated with Parkinson's disease.
- Benztropine is more specific than atropine regarding central effects.

Central uses:

- Pre-anesthetic medication
- Parkinson's disease (but benztropine (Cogentin)® is better)
- Motion sickness (but hyoscine (Buscopan)® is better)

1.1.5. Nicotine

It is an alkaloid from Tobacco leaves with ganglionic stimulant actions via N receptors having, in addition, the following central actions:

- Alertness followed by tranquilization.
- Skeletal muscle relaxation after short initial stimulation.
- Increases release of catecholamines and 5-HT leading to mood disturbances.

- Stimulates respiratory center:
  - Small dose reflexly via chemorecptors
  - Large dose directly
- Stimulates vasomotor center and CTZ.

1.1.6. Cocaine

It is an alkaloid from *Erythoxylon coca* leaves of local anesthetic activity with the following central actions:

- Cerebral cortex: stimulation in descending manner causing euphoria, elation, wakefulness and increased capacity to work. Prolonged use or large doses leads to cumulation of catecholamines due to inhibition of neuronal uptake-1 and inhibition of monoamine oxidase causing mood disturbances. Addiction finally established with symptoms of excitement, psychosis, epileptiform convulsions and typical withdrawal syndrome.
- Stimulation of respiratory, vasomotor, vagal and vomiting centers.

1.1.7. LSD

Lysergic acid diethylamide (LSD) is related to ergot alkaloids with the following central actions:

- Visual hallucinations.
- Psychotic reactions.
- Drowsiness, ataxia and motor incordination.
- Tolerance is rapidly acquired (tachyphylaxis).

Mode of action: LSD stimulates 5-HT receptors in CNS.

1.2. MEDULLARY STIMULANTS
"ANALEPTICS"

Def: these are the drugs which stimulate vital medullary centers especially when depressed.

Members: analeptics are classified according to their mode of action into three groups:

Direct analeptics	Reflex analeptics	Dual analeptics
Picrotoxin	Ammonia	Camphor
Leptazole	Lobelia	Nikethamide
Megimide		
Doxapram		

1.2.1 Direct medullary stimulants
1.2.1.1. Picrotoxin

Actions:

- Mainly ↑ respiratory, vasomotor, vagal & vomiting center.
- Large doses produce convulsions due to extension of action to cerebral & spinal cortices.

Mode of action:

- Anti-GABA, i.e. it inhibits the presynaptic inhibitory transmitter GABA (Gamma amino butyric acid).

Uses:

- Narcotic and hypnotic poisoning (3~6 mg, i.v.)

Limitations:

- Long latent period 15 minutes after i.v. injection.
- Short duration of action - Narrow safety margin

1.2.1.2. Leptazole (Cardiazole)

Actions:

- It mainly ↑ respiratory, vasomotor and vagal center.
- Large doses produce convulsions.
- It is also anti-GABA and shortens the time of neuronal recovery.

Uses:

- Hypnotic poisoning.
- Respiratory depression.

It differs from picrotoxin in the following:

- Faster onset of action
- Less toxic

1.2.1.3. Megimide (Bemegride)

- Powerful medullary stimulant, of quick onset but of short duration.
- Used in barbiturate poisoning and to arouse animals from anesthesia (50 mg, i.v., repeated every 10 minutes until arousal)

1.2.1.4. Doxapram (Dopram)

- It is the safest analeptic of wide safety margin (high therapeutic index)
- Mainly stimulates respiratory center.
- Used in post-anesthetic respiratory depression.

1.2.2. Reflex medullary stimulants

Def.: They stimulate medullary centers reflexly after local irritation elsewhere in the body.

Members:

- **Ammonia:** it irritates nasal mucosa after inhalation; it acts rapidly therefore used to awake comatosed patients.

- **Aromatic spirit of ammonia:** it irritates gastric mucosa after oral administration.

- **Lobelia:** It irritates carotid body after absorption stimulating respiratory center mainly.

1.2.3. Dual medullary stimulants

1.2.3.1 Nikethamide (Coramine)®

- Its analeptic action is less potent but of longer duration.
- It mainly stimulates respiratory center, in two ways:
  - directly on respiratory center by ↑ its sensitivity to CO_2
  - reflexly via carotid body by ↑ of chemoreceptors.
- Used in conditions associated with respiratory depression (0.5~1 gm as 25% soln., i.m or i.v.).

1.2.3.2. Camphor

- After s.c. or i.m. injection, it produces analeptic action.
- The analeptic action is attributed to:
  - local irritant effect and reflex stimulation of medullary centers.
  - direct medullary stimulation after absorption.
- Used externally as counter irritant with rubbing (camphor liniment 20% in turpentine oil), orally as carminative (aqua camphora), parenterally as analeptic in respiratory depression (1 ml of 20% oily solution, s.c.).

1.3. SPINAL CORD STIMULANTS

These are the drugs which specifically stimulate the spinal cord as:

STRYCHNINE

Actions:

CNS:

- It produces dose-dependent ascending stimulation of CNS.
- It sensitizes the sensory area, increasing sharpness of all special senses → alertness and hyperesthesia.
- It ↑ motor portion of spinal cord leading to convulsions in large dose.

DS:

- Bitter stomachic (very diluted solutions)
- Purgative by stimulation of Aurbach's plexus in intestine.

GS:

- Aphrodisiac action via stimulation of sexual centers in the spinal cord and its neurotonic action.

Mode of action:

- Anti-glycine, i.e. it blocks the postsynaptic inhibitory transmitter, glycine at its receptor level.

Uses:

- Decreased reflexes as nerve tonic.
- Debility or loss of appetite as general tonic.
- Chloralhydrate and barbiturate poisonings.
- Sexual impotency in males as aphrodisiac.
- Killing of stray dogs.

Toxicity:

• Symptoms:

- Similar to tetanus and the patient takes "opisotonus" position (Fig. 25).
- Legs and tail are rigidly extended as extensor muscles are stronger than flexors.
- Head and neck are driven upward and backward.
- Arched back
- Death may occur from asphyxia after 5 or 6 seizures.

• Treatment:

- Keeping the animal in a dark place away from external stimuli.
- Short acting barbiturate as Nembutal (for convulsions)
- Specific antidote like "mephenesin"(0.5~1gm, 1.v.) which increases the resistance of synapses in the spinal cord.
- Potassium permanganate 0.5% (to oxidize strychnine) or tannic acid 2% (to precipitate it) to prevent further absorption of the poison.
- Artificial respiration.

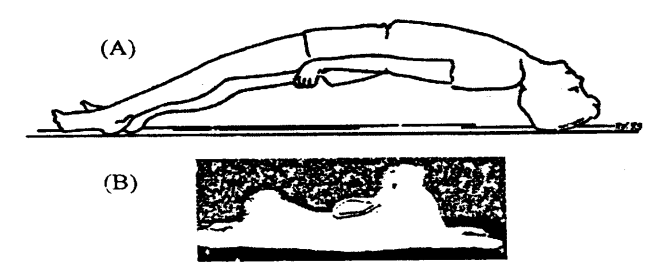


Fig. 25: A human (A) and a rabbit (B) showing opisotonus position during a seizure caused by strychnine toxicity.

2. CNS DEPRESSANTS

Def: these are drugs which depress or decrease the activity of different parts of CNS.

Classification:

They are classified according to their degree of CNS depression into:

1- Sedatives
2- Hypnotics
3- Anti-convulsants
4- Tranquilizers
5- Analgesics
6- Anesthetics

2.1. & 2.2. SEDATIVES & HYPNOTICS

Def:

Sedatives are the drugs which produce "sedation" (calmness) while hypnotics are the drugs which produce "hypnosis" (sleep).

Sedatives usually produce hypnosis when given in large doses.

Members:

- Barbiturates
- Chloralhydrate
- Xylazine
- Chlorbutol

2.1-2.1. Barbiturates & Chloralhydrate

- Small doses are hypnotics, look at anesthetics part

2.1-2.2. Xylazine

- It produces sedation, hypnosis, analgesia together with central muscular relaxation according to its dose.
- Most suitable for ruminants.

- Can be also used for horses but in large doses (not suitable because of economic reasons)

2.1-2.3. Chlorbutol

Actions:

- After topical application, it has local anaesthetic & antiseptic actions.
- After absorption, it has sedative effect and depresses ↓ vomiting and respiratory centers.

Uses:

- Externally as dusting powder for analgesia & antisepsis.
- Internally as gastric sedative (antemetic), in two ways:
    - Centrally by depressing vomiting center
    - Locally by its anesthetic effect on gastric mucosa

2.3. ANTICONVULSANTS

Def: These are drugs which have the ability to depress the convulsions.

Members:

Anticonvulsants are classified according to their mode of action into:

- **Non-specific:** which decrease all types of convulsions by general depression of CNS including:
    1. General anaesthetics (as barbiturates) which inhibit acetylcholine formation, in addition to raising the convulsive threshold of the motor cortices by facilitating GABAergic transmission and increasing Cl^- influx.

2. Na. Valporate (Depakine)® which increases GABA level within CNS via inhibition of GABA transmainase enzyme: in addition to blocking of central Na^+ and Ca^{++} channels.
3. Benzodiazepines as Diazepam (Valium)® and Clonazepam (Rivotril)® which facilitate GABAergic transmission via acting on their specific receptors.

- **Specific:** which decrease convulsions originated from certain parts of CNS by raising the convulsive threshold of certain motor areas via stabilizing or hyperpolarizing the neuronal cells of that part; including:
  1. Phenytoin Na. (Epanutin)®, Carbamazepine (Tegretol)® and primidone (Mysoline)®: which decrease convulsions originated from the cerebral motor cortex. They block Na^+ channels.
  2. Troxidone (trimethadione): used for treatment of epileptiform convulsions caused by picrotoxin.
  3. Mephensin: specific on spinal cord motor cortex.

Uses of anticonvulsants:

- Epilepsy الصرع
- Travel sickness (primidone)
- Poisoning of a convulsant drug.

2.4. TRANQUILIZERS "ATARACTICS"

Def: These are the drugs which make the patient less responsive to outside stimulations.

- In Vet. Practice, they are used mainly for handling and restraint of vicious animals.

- Also, they are used before anesthesia (pre-anesthetic medicaments) to reduce the dose of used anesthetic.

Members:

Tranquilizers are classified according to the nature of action into:

Major tranquilizers (Anti-psychotics; Neuroleptics)	**Minor tranquilizers (Anxiolytics; Anti-anxiety)**
Are the drugs which have ataractic effect and normalize the psychotic conditions as hysteria and schizophrenia including: - Phenothiazine derivatives as: . Chlorpromazine (largactil)® . Acepromazine . Promazine . Perphenazine - Butyrophenones as: . Haloperidol (Safinace)® - Rawolfia alkaloids as: . Reserpine - Other as: . Thioridazine (Melleril)® . Trifluperazine (Stelazine)® . Sulpiride (Dogmatil)®	Are the drugs which have ataractic effect and remove anxiety, tension and insomnia including: - Propanediol derivatives as: . Meprobamate - Diphenylmethane derivatives as: . Hydroxyzine (atarax)® - Azapirones as: . Buspirone (BuSpar)® - Benzodiazepine derivatives as: Diazepam (Valium)® Clonazepam (Rivotril)® Lorazepam (Ativan)® Chlorazepate (Tranxene)® Alprazolam (Xanax)®

2.4.1. Meprobamate

- It depresses polysynaptic motor transmission in spinal cord via blocking the conductance of impulses through the spinal interneurons.
- It is good relaxant for both skeletal & smooth muscle.

2.4.2. Azapirones

Buspirone (Buspar)®

- Buspirone (BuSpar)® is an anxiolytic agents that can relieve anxiety in doses that do not cause sedation.
- The action of buspirone is mediated through interaction with 5-HT at $5\text{-}HT_1$ receptor, where it acts as a partial agonist.

2.4.3. Bezodiazepines

- The benzodiazepines constitute the most commonly used group of anxiolytics nowadays, examples are:
  - Alprazolam (Xanax)®
  - Chlorazepate (Tranxene)®
  - Diazepam (Valium)®
  - Lorazepam (Ativan)®
  - Clonazepam (Rivotril)®
- Benzodiazepines potentiate GABAergic neurotransmission in CNS. This enhancement is thought to occur at the postsynaptic $GABA_A$ receptor complex.

2.4.4. Diphenylmethane derivatives

Hydroxyzine (Atarax)®

- Atarax is unrelated chemically other anxiolytics.

- It is not a cortical depressant, but its action may be due to a suppression of activity in certain key regions of the subcortical areas of the CNS. In addition, it has also has antihistaminic and muscle relaxant effects.
- It is indicated in anxiety (as tranquilizer), pruritis (as antihistaminic), bronchial asthma (as muscle relaxant and antihistaminic) and in pre-anesthetic medication (as sedative).

General therapeutic uses of minor tranquilizers:

- Anxiety.
- Insomnia.
- Epilepsy and Seizures.
- For sedation, amnesia, and anesthesia.
- Withdrawal syndrome.
- Pre-anesthetic medication

2.4.5. Phenothiazine derivatives

2.4.5.1. Chlorpromazine

Actions:

- CNS: antipsychotic and marked depressant to brain stem (medulla, reticular formation, CTZ) via interference with dopamine at the level of D_2 receptor.
- Other: Multiple actions like:
  1. Antiemetic, antihistaminic, antispasmodic and adrenoceptor blocking, and atropine-like actions
  2. Hypotensive and hypothemic actions.

Uses:

- Pre-anesthetic medication.
- Handling of vicious animals.

- Specific diseases as tetanus, colic & pruritis.
- Persistent hiccup via relaxation of muscular portion of the diaphragm.
- Vomition but not in pregnancy as it is teratogenic.

2.4.5.2. Acepromazine

More potent than chloropromazine, used in horse

2.4.5.3. Promazine

- Less potent, therefore safe.
- Recommended for use in all farm animals

2.4.5.4. Perphenazine

- More potent as anti-emetic.
- Used for travel sickness.

N.B. Other major tranquilizers are rarely used in Vet. practice...

2.5. ANALGESICS

Def: These are the drugs which relieve pain.

Classification:

They are classified according to their nature of action into:

Narcotic	Non-Narcotic (Antipyretic)
They include drugs which relieve pain and produce euphoria and drowsiness	They include drugs which relieve pain and reduce high body temperature
They may cause addiction	They are non- addictive
Examples: morphine and its derivatives	Examples: salicylates and related drugs

2.5.1 NARCOTIC ANALGESICS

- The source of narcotic analgesics is opium أفيون which is the dried exudate of *Papaver somniferum* plant.
- Opium contains morphine and other alkaloids which can be subdivided into:-

Phenanthrene derivatives	Isoquinoline derivatives
They mainly have narcotic analgesic effect as: - Morphine - Codeine	They mainly have a smooth muscle relaxant effect as: - Papaverine

2.5.1.1 PHENANTHRENE DERIVATIVES

2.5.1.1.1. Morphine

Actions:

CNS:

- Initial stimulation followed by depression except in dog which devoids the initial stimulation. While in cat, stimulation persists for longer time.
- After administration, there is restlessness, salivation, emesis, defecation and miosis, then hypothermia and narcosis. In man, it is associated with euphoria and sense of pleasure due to relief of pain.
- Vagal, oculomotor and CTZ are initially stimulated and later depressed.
- Respiratory, vasomotor and cough centers are depressed.
- After repeated administration, acquired tolerance and dependence are induced.

DS:

- Strong constipating effect due to spasm in muscle and sphincters and inhibition of defecation reflex.
- Biliary retention due to spasm in biliary muscle and sphincter of Oddi.

US:

- Urine retention due to the hypotensive effect and sphincter spasm.

CVS:

- Hypotension due to vasomotor center depression and cutaneous vasodilatation.

GS:

- Morphine passes placental barrier and may cause neonatal asphyxia.

Skin:

- Flushing and itching due to cutaneous vasodilatation and histamine release.

Eye:

- Miosis (P.P.P = pin point pupil)

Mode of action: activation of opiate (μ = mu, δ = delta and κ = kappa) receptors in CNS and peripheral tissues.

Uses:

- Pre-anaesthetic medication.
- Spasmodic colic.
- Dry cough.
- Cases associated with sever pain as fractures and cancers.

Dose: 10 mg s.c., or i.m. or 5 mg i.v. repeated every 6-8 hours after operations.

2.5.1.1.2. Codeine

- Similar to morphine.
- Less potent (1/5 of morphine).
- Less addictive.
- Less constipating.
- Used mainly in dry cough & for analgesia.

2.5.1.2. ISOQUINOLINE DERIVATIVES

Papaverine

- It has less narcotic effect.
- It is powerful relaxant to smooth muscle.
- Used mainly in various types colic and embolism.

In addition to opium-derived alkaloids, semisynthetic and synthetic derivatives have been derived including:

Semisynthetic morphine substitutes, including:

- **Diamorphine (Heroin)**
- **Apomorphine**

Synthetic morphine substitutes, include:

- **Methadone**
- **Diethylthiambutan**
- **Meperidine**
- **Fentanyl**
- **Etorphine**

Diamorphine (Heroin)

- Made by acetylation of morphine (diacetyl morphine)
- Absorbed from all routes including nasal mucosa
- It passes blood brain barrier causing rapid deterioration of morals and health of the recipient.
- Rarely used therapeutically.

Apomorphine

- Made by treating morphine with mineral ac. .s reducing its narcotic activity and increasing its stimulant effects.
- Mainly stimulates vomiting center via CTZ.
- Used to induce emesis (0.08 mg/kg s.c.).

Methadone (Amidone) & Diethylthiambutane (Themalon)

- Synthetic narcotic analgesic similar to morphine

Meperidine (Pethidine)

- Synthetic morphine substitute.
- Less potent (1/10) than morphine.
- Mainly used as antispaamodic.

Fentanyl

- More potent narcotic analgesic (50x as morphine) but short acting.
- Chemically related to meperidine

Etorphine

- Synthetic compound 100 times as potent as morphine.

N.B. Loperamide (Imodium)®, of no CNS effects and Diphenoxylate (Lomotil)®, of mild CNS effects are selective opiate agonists on G.I.T and thus very useful in treatment of severe diarrhea.

MORPHINE ANTAGONISTS

Nalorphine (Lethidrone)

Competitive antagonist to morphine & its substitutes.

Naloxone (Narcen)

Competitive antagonist to morphine & etorphine.

Diprenorphine

Specific antagonist to etorphine.

2.5.2. NON- NARCOTIC ANALGESICS
"ANTIPYRETIC ANALGESICS"
"NON-STEROIDAL ANTI-INFLAMMATORY DRUGS"
(NSAIDS)

Def: these are the drugs which relieve pain and able to reduce fever and inflammation.

Classification:

According to the nature of their action, they are classified into:

A. Specific

- The drugs which remove the cause of inflammation and fever as antibiotics

B. Non-specific

- Drugs which normalize feverish temperature and milden inflammation.
- They are subdivided into:

Central	Peripheral
Act on heat regulating center causing: • Vasodilatation of skin vessels • Increased sweating • Mobilization of fluids from tissues to blood	Act mechanically on peripheral blood vessels.
They are further classified according to their chemical structure into: **1-Salicylates & salicylates derivatives:**	Examples: Fomentations Cold baths

- Acetyl salicylic acid (Aspirin)® - Salicylic acid - Na salicylates **2- Aniline (paraminophenol) derivatives:** - Acetanilide - Phenacetin - Paracetamol (Abimol)® **3- Pyrazolone derivatives:** - Dipyrone (Novalgin)® - Phenylbutazone (butazolidin)® - Suxibutazone - Isopyrin **4- Propionic acid derivatives:** - Ibuprofen (Brufen)® - Ketoprofen (Ketofan)® - Naproxyn (Naprosyn)® **5- Fenamic acid derivatives:** - Fenamic acid (Ponstan)® - Flufenamic acid (Arlef)® **6- Acetic acid derivatives:** - Diclofenac (Voltaren)® **7- Indole derivatives:** - Indomethacin (Indocid)® **8- Oxicams:** - Prioxicam (Feldene)®	

1. Salicylates and salicylates derivatives

Salicylic acid

- Very irritant, so used only as Keratolytic (up to 30%) and fungistatic.
- Also used for promotion of hair growth by irritation of scalp and enhancing its blood supply (up to 10%).

Na salicylates

Actions:

- Analgesic via inhibition of pain center in the thalamus.
- Antipyretic via its effect on heat regulating center (HRC) producing heat loss (vasodilatation of cutaneous blood vessels and increasing sweating).
- Anti-inflammatory by ↓ prostaglandin synthesis via irreversible inhibition of cycloxygense pathway). Also, it releases ACTH which liberates endogenous cortisone.
- ↑ respiratory center directly and increasing production of CO_2 by increasing cellular metabolism → alkalosis.
- ↑ urinary excretion of uric acid by reducing its tubular reabsorption (uricosuric action; in doses over 5 gm/day).
- Irritates gastric mucosa with epigastric pain, nausea and vomiting and may be ulceration.
- Prolongs bleeding time by its antiplatelet aggregation action.
- Prolongs coagulation time by inhbiting utilization of Vit. K.
- Small decreases blood sugar level by enhancing glucose utilization by peripheral tissues; may be useful in diabetics.

Larger doses should be avoided in them due to depletion of muscle and liver glycogen with result of hyperglycemia.

Uses:

Systemically:

- **Cases associated with pain & fever for analgesia & antipyresis.**
- **Rheumatism & muscular & joint pain.**
- Gout.
- Thrombosis.

Locally:

- Removal of warts (20% salicylic acid in collodion).
- Mycotic infection with benzoic acid.
- Lumbago and musculoskeletal pain as liniment or cream or oil (methyl salicylate as wintergreen oil).

Acetyl salicylic acid

(Aspirin)®

- Similar to salicylate but more powerful.

2. Aniline derivatives:

Phenacetin & Acetanilide

- Old drugs which are acetylated into paracetamol inside the body by acetylaing enzymes.
- Lack of acetylating enzymes in some species like dogs and cats render these drugs dangerous due to formation of met-haemoglbin.

Paracetamol

- Now used instead of phenacetin & acetanilide.
- Antipyretic analgesic drug without peripheral anti-inflammatory activity due to ↓ of PG synthesis in the brain mainly.
- No uricosuric action.
- No gastric irritation.
- No respiratory action.
- Used for treatment of headache and other pains.
- Safe in pregnancy & peptic ulcer.

3. Pyrazolone derivatives

Phenylbutazone (butazolidin)®

- Antipyretic analgesic used to relieve pain of skeletal muscle
- May be used therapeutically but it is not suitable because of many disadvantages including:
    - Irritant to gastric mucosa.
    - Na & Cl retention leading to edema.
    - Contraindicated in heart, liver & kidney diseases.
    - Slowly excreted in man leading to chronic poisoning with symptoms of:
        - Nausea & vomiting
        - Edema
        - Skin reactions
        - Damage of heamopoietic organs.

Suxibutazone &Isopyrin

- Antipyretic analgesic related to phenylbutazone & thus similar to it

<u>N.B.: All of the following groups share the following properties:</u>

- ***Inhibit <u>both</u> central and peripheral cyclooxygenases.***
- ***Anti-inflammatory and antirheumatic.***
- ***Antipyretic analgesics.***
- ***<u>Not</u> uricosurics.***
- ***Displace other drugs from plasma protein binding sites.***
- ***Produce gastric irritation; should be avoided in gastric ulcer.***
- ***Useful in arthritis.***

4. Propionic acid derivatives

Ibuprofen (Brufen)®, Ketoprofen (Ketofan)®, Naproxyn (Naprosyn)®

- Analgesic antipyretic drugs.
- They block both peripheral and central cyclooxygenases.
- <u>Potent</u> anti-inflammatory and antirheumatic.
- Not uricosurics.
- Irritate gastric mucosa.
- Care must be taken as they are cumulative due to strong plasma protein binding and can displace other already binding drugs.

6. Fenamic acid derivatives

Fenamic acid (Ponstan)®, Flufenamic acid (Arlef)®

- Analgesic antipyretics similar to propionic acid derivatives with <u>potent</u> anti-inflammatory actions but they may cause diarrhea.
- They act by: ↓ tachykinin synthesis (SP).

↓ Migration of macrophages to inflammed site

↓ PG release

7. Acetic acid derivatives

Diclofenac (Voltaren)®, (Cataflam)®

- Similar to propionic acid derivatives but they are concentrated 4 time in synovial fluid more than plasma.
- Enhance incorporation of arachidonic acid (which is the substrate of cycooxygenase and lipoxygenase) into triglycerides and therefore block formation of both prostaglandins and leukotrienes because of inavailability of the substrate molecule.

5. Indole derivatives

Indomethacin (Indocid)®

- Potent analgesic antipyretic.
- Potent inhibitor of both peripheral and central cyclooxygenases.
- Potent anti-inflammatory actions greater than salicylates and hydrocortisone.
- Highly bound to plasma proteins.
- Not uricosuric.

8. Oxicams

Prioxicam (Feldene)®

- Similar to propionic acid derivatives but of long half-life up to 36 hours or more. So, they should be taken only once daily.

N.B.: Dipyrone = Metamizol (Novalgin)® is antipyretic analgesic with anti-inflammatory properties without uricosuric action. However, it has a bad site effect of inhibition of bone marrow that leads to agranulocytosis and decreased body defense mechanisms. So its use in therapeutics has been limited in many countries.

According to their relative activities, NSAIDS can be classified into the following 3 groups (Table 10):

Table (10) classification of NSAIDS according to their anti-inflammatory activity

Analgesics with **weak** anti-inflammatory action:	- Paracetamol.
Analgesics with **moderate** anti-inflammatory action:	- Propionic acid derivatives. - Fenamic acid derivatives.
Analgesics with **potent** anti-inflammatory action:	- Salicylates. - Pyrazolones. - Acetic acid derivatives. - Indole derivatives. - Oxicams.

2.6. ANAETHESIA AND ANAESTHETICS

Def.: Anaethetics are the drugs which produce anaesthesia (which means loss of sensation)

Anaethesia is classified into:

Local anaesthesia	General anaesthesia
A condition of temporary loss of pain sensation in a localized part by reversible paralyzing the peripheral nerves supplying that part.	A condition of reversible depression of CNS characterized by : - Total loss of consciousness. - Loss of sensations & loss of motor activity without dysfunction of vital centers in the medulla.

An ideal local anesthetic should be:

- Soluble in water
- Non-irritant
- Of rapid onset
- Of suitable duration
- Slowly absorbed from the part
- Of low toxicity if absorbed
- Non-addictive

While an ideal general anaesthetic should have the following characteristics:

- **Easily administered**
- **Non- irritant**

- Rapid action with least struggling
- Provides good CNS depressant action
- Provides good CNS relaxant action
- Rapid recovery
- Wide safety margin
- Has available antidote, just in case of toxicity
  - **If volatile, in addition, it should be:**
    - **Chemically stable upon exposure to air**
    - **Non-inflammable or explosive**
    - **Pleasant odor**

No single general anesthetic has **all** these characters, so some supportive drugs may be given before administration of the anesthetic to obtain good balanced anesthesia, these drugs are called "pre-anaesthetic drugs" and the process is called **"pre-anaesthetic medication"**

Pre-anesthetics:

Are the drugs which are given prior to an anaesthetic to make anaesthesia safer and agreeable to the patient. These drugs include:

1- Sedatives, hypnotics, tranquilizers, anticonvulsants and analgesics. They are used as pre-anesthetics to:

- Lower the dose of the anesthetic required.
- Reduce muscular tone.

2- Atropine and atropine- like drugs to:

- Reduce the bronchial and salivary secretion and thus avoid suffocation and postoperative bronchopneumonia.
- Protect against heart failure
- Stimulate respiration
- Contribute in CNS depression as hyoscyamine which has CNS-depressant action.

3- Muscular relaxants to: Avoid motor activity
as; tubucurarine, succinylcholine & suxamethonium.

Theories explaining the possible mechanisms of action of general anaesthetics.

The exact mechanism of action of general anaesthetics is yet unknown, however, there are many theories reported:

1- **Colloid theory (Claude & Bernard 1875):**
This theory hypothesize that an anesthetic agent causes reversible change of the cellular protoplasm of nerve cell into colloids which inhibit nerve conduction.

2- **Lipid solubility theory (Mayer, 1894-Overtone, 1901 theory):**
This theory hypothesizes that a general anaesthetic must be lipid soluble and the greater oil/water partition coefficient, the greater its anestehtic action. This will allow easy entrance of these drugs into lipoid membrane of nerve cell function.

3- **Surface tension theory (Traube 1904):**

This theory hypothesizes that there is a relationship between general anesthetic activity of a drug and its ability to reduce surface tension of nerve cells.

4- **Cell permeability theory (Hober 1907):**

This theory hypothesizes that the presence of an anesthetic in contact with the nerve cell membrane may disturb the normal permeability with no depolarization and thus conduction is impeded.

5- **Adsorption theory (King 1930):**

This theory hypothesizes that a general anesthetic drug molecules concentrate onto the nerve cell membrane inhibiting depolarization and conduction.

6- **Biochemical theory (Quastel, 1952 & Nilsson, 1970):**

This theory hypothesizes that a general anesthetic may inhibit some metabolic enzymes in the nerve cell like cytochrome reductase disturbing some intracellular biochemical processes which are responsible for formation of high energy phosphate bonds or utilization of oxygen by a nerve cell depressing its function.

7- **Neurophysiological theory (Larabee, 1952):**

This theory hypothesizes that a general anesthetic may depress reticular formation (mesodiencephalic activating MDAS) which is responsible for wakefulness.

8- **Clathrate theory (Pauling & Miller 1961):**
This theory hypothesizes that molecules of a general anesthetic will be enclosed inside cage-like water crystals. These structures are called "clathrates" which interfere with the electrical conduction through the nerves.

9- **Physicochemical theory (Miller & Seeman, 1972):**
This theory hypothesizes that a general anaesthetic my alter the conformation of the lipoid membrane or its aqueous pores of a nerve cell disturbing its function.

Stages of general anesthesia.

"Induction" i.e. the time elapsed between anesthetic administration and complete anesthesia has been divided into 3 stages by Guedel (1951). During this time, the depth of anesthesia increases gradually until the patient becomes completely unconscious while medullary centers are still functioning properly; at that time an operation can be performed. If a large dose of an anesthetic is given or its time is prolonged more than what is needed, a 4th phase occurs in which medullary centers start to fail and death may follow.

After operation and successful anesthesia, the patient starts to wake up gradually passing with the same three stages in a reverse manner along what is called "Recovery".

Please see table (11) for complete description of general anesthesia.

Table (11) Stages of general anesthesia

	Excitement stage	Delirium stage	Anesthetic stage			Recovery stage	Medullary paralysis stage
			Plane 1	Plane 2	Plane 3		
CNS depression	Sensory cortex	Motor cortex	Midbrain & sp.cd	Sp.cd	Sp.cd	Reversal return	Medullary centers
Respiration	Rapid, deep	Rapid, very irregular	Slow, regular	Slow, regular	Shallow, abdominal	,,	Weak, shallow, irregular
Pulse & blood pr.	Rapid pulse & elevated bl.pr.	Rapid pulse & elevated bl.pr.	Normal pulse & normal bl.pr.	Lower pulse & lower bl.pr.	Rapid but weak pulse & low bl.pr.	,,	Weak pulse, fall in bl.pr.
Mucous membrane	Normal, flushed	Flushed	Flushed, normal	Normal	Normal, pale	,,	Cyanotic
Skeletal m. tone	+	++ irregular	±	-	-	,,	---
Eye pupil	Dilated	Dilated	Normal	Normal	Constricted	,,	Dilated
Eye movement	Moving	Roving	Roving	Fixed	Fixed	,,	Fixed & lusterless
Eye lid	Opened	Opened	Opened	Closed	Closed	,,	Closed
Corneal reflex	+	+	+	-	-	,,	--
Pedal reflex	+	+	±	-	-	,,	--
Cough reflex	+	+	+	-	-	,,	--

Methods of administration of volatile anesthetics:

1- Open method:

A piece of cotton or gauze is soaked in the volatile anaesthetic solution and placed in a mask covering the nose and mouth of the patient.

2- Positive feed method:

An anesthetic is given by passing the inspired air through a bottle containing the anaesthetic solution and a conical rubber mask.

3- Closed method

Anaesthetic is given by special anaesthetic machine which accurately controls the concentration of anesthetic and oxygen required.

Classification of anesthetics

General		Local
Volatile	**Non-Volatile**	**As:**
1- Liquids with low boiling points as:	**1- I.V. as:**	**1- Aminoesters:**
. Chloroform	. Chloralhydrate	- Cocaine
. Ether	. Barbiturates	- Procaine
. Vinyl ether	. Ketamine	- Amethocaine
. Trichloroethylene	. Alphaxolone	- Chloroprociane
. Halothane		- Benzocine
. Enflurane & Isoflurane		**2- Aminoamides:**
. Methoxyflurane	**2- Rectal as:**	- Lignocaine
2- Gasses stored under pressure as:	. Avertin	- Mepivacaine
. Nitrous oxide	. Paraldehyde	- Bupivacaine
. Cyclopropane	(Old fashioned)	- Ropivacaine
. Ethyl chloride		- Etidocaine.
. Carbon dioxide		- ...etc,

Chloralhydrate

Def: Intravenously administered drug being converted in the body into trichloroethanol which is responsible for CNS depression.

Action:

- Small dose produces sedation and hypnosis while large dose produces narcosis and general anaesthesia.
- It is dangerous as it has narrow safety margin.

Uses:

- Pre-anaesthetic medication
- Colic as antispasmodic
- To control convulsions with bromide

Barbiturates

Def.: Barbiturates are derivatives of barbituric acid "malonyl urea" which is the product of:

Urea + Malonic acid → Barbituric acid "Malonyl urea"

Members:

Barbiturates are classified according to their duration of action into 4 groups. Please look at table (12) for the members of each group and their properties.

Actions:

CNS: - Non- specific CNS depressants

- CNS depression is proportional to the dose
- Has prominent anti-convulsant action

M.O.A. as CNS depressant;

- ↓ Cytochrome reductase
- ↓ Reticular Formation
- ↓ ACh formation which is an excitatory transmitter in CNS
- ↑ the threshold of spinal reflexes (GABAergic facilitation)

RS:

- Barbiturates depress RC centrally and ↓ its sensitivity to CO_2

Table (11): Memebrs and properties of barbiturates

	Long acting	Medium acting	Short acting	Ultra-short acting
1. Duration of CNS depression	12-24 h (long)	6-12 h (medium)	3-6 h (short)	1/4-2 h (ultrashort)
2. Members	Phenobarbitone Methylbarbitone Barbitone	Allobarbitone Amobarbitone Probarbitone Hexabarbitone	Pentobarbitone Secobarbitone	Thiopentone Thiobarbitone Hexobarbitone
3. Ionization	++++	+++	++	+
4. Lipid solubility.	+	++	+++	++++
5. BBB passage	+	++	+++	++++
6. Onset of action	+	++	+++	++++
7. Absorption from GIT	+	++	+++	++++
8. Plasma protein binding.	+	++	+++	++++

DS:

- Barbiturates have spasmolytic action by direct inhibition of smooth muscle
- ↓ vomiting reflex
- ↓ gastric and pancreatic secretion

CVS:

- Hypnotic dose has no effect
- Anaesthetic dose ↓ blood pressure by:
    - ↓ Vasomotor centers.
    - Relaxation of blood vessel smooth muscles

Urogenital system:

- Hypnotic dose has no effect.
- Anesthetic dose ↓ urination via:
    - Hypotension
    - ↑ ADH
- Anesthetic dose ↓ uterine contractility.

Uses:

- Insomnia (long and intermediate acting barbiturates).
- Surgical operations (short and ultra-short acting barbiturates).
- Epilepsy and convulsions as tetanus & strychnine toxicity.
- Pre-anaesthetic medication.

Toxicity of Barbiturates:

Type	Acute	Chronic
Cause	Due to overdose (during anesthesia or intentional suicide)	Due to prolonged administration of long acting barbiturates
Symptoms	-Respiratory depression - Sluggish reflexes - Hypothermia & hypotension - Cyanosis - Death due to bronchopneumonia	- Incoordination - Weakness - Tremors
TTT	- Gastric lavage - Artificial respiration & Carbogen inhalation - Antibiotics to prevent pulmonary complications - Vasoconstrictors, plasma, saline transfusion. - CNS stimulants as picrotoxin	- Gradual cessation of the drug. - Gradual use of CNS stimulants.

Ketamine

- Anaesthetic in cat by i.m. injection
- Short duration of action (45 min)

Alphaxolone

- Anaesthetic in cat by i.v. & i.m. routes
- Not suitable for dogs as it releases histamine

Volatile anaesthetics

(Table 12) Liquids with low boiling points

	Chloroform	Ether	Vinylether	Trichloroethylene
General properties	-colorless -volatile liquid -boiling point 60°C -noninflammable -irritant -upon exposure to air → phosgene gas -decompose by light	-colorless -vol. liquid -boiling point 37°C -highly inflammable -irritant -upon exposure to air → irritant peroxides ---	-colorless -vol. liquid -boiling point 50°C -noninflammable -nonirritant -stable ---	-blue -vol. liquid -boiling point 87°C -noninflammable -less than chloroform -upon heating → phosgene gas ---

Actions: **CNS**	- Gen ana. 3x as ether - Narrow safety margin. - rapid induction & recovery	- Very good gen. an. **- reasonable** **- fairly rapid**	- potent short gen. an. - wide - rapid induction & recovery	- good gen. an. - ↑ than chloroform - fairly rapid
CVS	- during induction: it sensitizes the myocardium to the action of NE. - during anaesthesia: it decreases bl. Pr by: . ↓ vasomotor center . ↓ vascular smooth muscle . ↓ cardiac output	**- does not sensitize** **- during anaesthesia: it slightly rises blood pressure by:** **. ↓ vagal center** **. ↑ cardiac output** **. vasoconstriction.**	- does not sensitize - no effect	- during induction: it sensitizes the myocardium to the action of NE. - As chloroform.

RC	- ↑ salivary & bronchial secretions - ↓ Bronchial sm. Muscle - ↓ Cilia leading to bronchopneumonia - ↓ RC after inhalation.	- ↑ salivary & bronchial secretions - bronchospasm and laryngospasm -↓ RC after inhalation	- No irritation to salivary & bronchial secretions.	Less irritant than chloroform
DS	- ↑ saliva - ↓ GI sm. muscle - Carminative - emetic by: . ↑ vomiting center . irritate gastric mucosa	- as chloroform - does not ↑ vomiting center	Slight effect	As chloroform but lesser

US	- ↓ urination by: . ↑ADH release . Hypotension	- ↓ urination by: . ↑ ADH release .Vasoconstriction	Slight effect	As chloroform but lesser
Uterus	Excellent relaxation	Not	Not	Good
Sk. Muscle	Perfect relaxation	Less than chloroform	As ether	Poor
Ther. Uses	Surgical operations as anaesthetic	Surgical operations	- Minor operations - Induction	- Minor operations - Induction
Contraindications	- Liver disease - lung & renal disease - Acidosis	- lung & renal disease - Acidosis	- lung & renal disease - Acidosis	- lung & renal disease - Acidosis
Toxicity	Hepatotoxicity; either:	- convulsions of unknown cause	- rare	- Nephrotoxicity - Hepatotoxicity

	- Acute: . cardiac arrest . hypotension . hypothermia . postoperative shock - Chronic: . jaundice . liver atrophy . acidosis . vomiting	- respiratory complications - suffocation due to laryngospasm		- Cardiac arrest

(Table 13-a) Gases stored under pressure

	Ethylchloride	Nitrous oxide	Cyclopropane
General properties	-colorless -with ethereal odor -Very low boiling point 12°C -Highly inflammable	-colorless -sweat taste -gas -Non	-colorless -odorless -gas -Non
Anaesthesia	- rapid and short but not deep (Few minutes). - incomplete muscular relaxation	- Rapid and not deep (Few seconds) -incomplete muscular relaxation	- Rapid (Few minutes) -incomplete muscular relaxation
Ther. Uses	-Minor operations in small animals as anaesthetic - local anaesthetic	Maintenance of anesthesia	- Minor operations in small animals
Toxicity	-difficult respiration -cardiac arrest due to sensitization to catecholamines	-safe	- safe

(Table 13-b) Gases stored under pressure (continued)

	Halothane	Enflurane	Isoflurane	Methoxyflura
General properties	-colorless -volatile liquid -pleasant odour -non-inflammable -decomposes in light	-colorless -vol. liquid -pleasant odour -non-inflammable ---	-colorless -vol. liquid -pleasant odour -non-inflammable -isomer of enflurane	-colorless -vol. liquid -sweet odour -non-inflammable ---
CNS	-rapid induction and recovery -weak analgesic	-rapid induction and recovery -seizures may occur	-very rapid induction and recovery -analgesic	-slow induction and recovery -potent analgesic
CVS	-bradycardia (stage I): . ↑ vagal tone . ↓ SA node -arrhythmia (satage II): . sensitize myocardium to catecholamines -hypotension (satge III):	-less arrhythmia -less hypotension	-less arrhythmia -less hypotension than halothane	-cardiac arrhythmia -hypotension

	. ↓vasomotor center . Ganglionic blocker . α blocker . direct vasodilatation . direct cardiac ↓ -useful in plastic and neurosurgery			
Respiration	-respiratory depression -bronchodilator so useful in asthmatics	-respiratory depression	-respiratory depression -irritant to bronchi	-non-irritant -less respiratory depression
Sk. Muscle	+ -moderate relaxant -inadequate in abdominal surgery	++ -better relaxant -↑ non-depolarizing N-M blockers	+++ -marked relaxant -↑ non-depolarizing N-M blockers	++++ -excellent relaxant
Uterus	-relaxant -not in labour	-relaxant -not in labour	-relaxant -not in labour	-relaxant -useful in obstetric analgesia

Local anesthesia is safer and should be applied whenever possible as its effect is local or regional with lesser effects on CNS but mainly peripheral on nerves supplying the part under operation.

Def.: Local anesthesia is a condition of temporary loss of pain sensation in a localized part by reversible paralyzing the peripheral nerves supplying that part.

Methods of induction of local anesthesia:

1. **Cooling:** by refrigeration, volatile drugs, or dry ice (CO_2).
2. **Inducing ischemia:** by tourniquet.
3. **Acupuncture** الابر الصينية : by using golden or stainless steal needles pricked at special sites for each region. This stimulates opioidergic nerves supplying the region to release endorphins producing analgesia.
4. **Using specific local anesthetic drugs** which is discussed in this part.

Methods of administration of local anesthetics:

1- Topical or surface application:

Here, the local anesthetic is applied to the skin or mucous membranes in the form of spray as ethylchloride or ointment as cocaine, amethocaine, or cinchocaine. The topically applied anesthetic paralyzes the sensory nerve endings at the skin or membrane surface blocking conduction.

2- Infiltration or field anaesthesia:

Here, the local anesthetic is distributed subcutaneously by making several depositions of its solution using long needle.

The anesthetic diffuses into the surrounding tissue and anesthetize the nerve endings and fibers of the applied part. Examples are procaine and cocaine.

3- Nerve block or regional anesthesia:

A local anaesthetic solution as procaine is injected around a superficial nerve trunk(s) supplying the site of operation. Examples are:

- Blocking of palmer or planter nerves in diagnosis and treatment of lameness.
- Paravertebral anesthesia: where the anesthetic solution is applied to spinal nerves as they emerge from the intervertebral foramina. Blocking of the last three thoracic and the first two lumbar nerves is used for labarotomy .

4- Epidural anesthesia:

Where a local anesthetic solution as procaine is injected into the epidural space at the level of lumbosacral region via lumboasacral space or 1st or 2nd intercocygeal spaces. It is useful for operations in the lower or caudal part of the body as Caesarian section.

Mode of action of local anesthetics:

Local anesthetics are weak bases that remains unionized in the weak alkaline pH and thus penetrate through the lipoid membrane of the nerve producing local anaesthetic effect by one of the following mechanisms:

- Preventing impulse conduction through the nerve by preventing depolarization directly via interference with Na^+ channel permeability induced by action potential.

- Preventing impulse conduction through the nerve by preventing depolarization indirectly via displacement of Ca^{++} ions from their binding sites on the nerve cell membrane inhibiting cell function.

Classification of local anesthetics

The typical local anesthetic molecule consists of a benzene ring linked by an intermediate chain to a tertiary amine end (Fig. 26). The tertiary amine is a base gives alkaline property to the anesthetic. Depending on the type of the intermediate chain, local anesthetics are classified into 2 groups:

1. **Aminoesters** which have an ester link between the benzene ring and amine end as cocaine, procaine, chloroprocaine, benzocaine and tetracaine.
2. **Aminoamides** which have amide link between the benzene ring and the amine - end as lidocaine, mepivacaine, bupivacaine, ropivacaine and etidocaine.

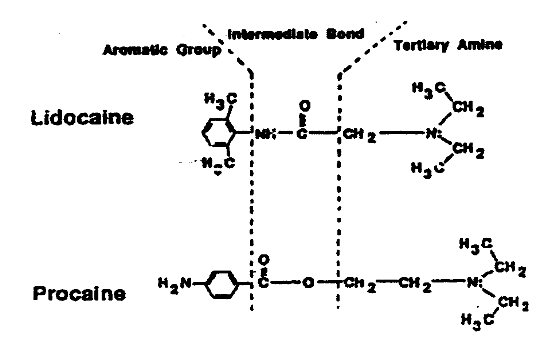


Fig. 26: Local anesthetics consist of hydrophilic and lipophilic ends connected by a hydrocarbon chain. The connecting chain is either an amide as lidocaine, or an ester as in procaine. *(Cited in H. R. Adams, 8th Ed.)*

Individual local anesthetics

Cocaine

Actions: it is local anaesthetic of long duration because:

. it inhibits MAO,

. it inhibits uptake of catecholamines.

Because of these two reasons, cocaine prolongs its own action due to vasoconstriction.

Uses:- Topical anaesthesia for mucous membrane and cornea

Disadvantages:

- addictive
- initial stimulation of CNS followed by depression
- death may occur due to respiratory paralysis

Procaine (Novocaine)

- It is a derivative of PABA (para-amino benzoic acid), therefore its use should be avoided in patients on sulphonamide therapy as it is metabolized in the body into PABA which is an antagonist to sulpha drugs.

- Commonly used for infiltration and epidural anaesthesia

- Alone or with noradrenaline as it doesn't cause vasoconstriction.

Amethocaine (Pantocaine)

- Used for topical anesthesia of skin, mucous membrane and cornea as solution or ointment.

-Also in otitis to relieve itchy pains.

Lignocaine (Xylocaine)

- commonly used for injection or topical local anaesthesia.

- of prolonged action as it is resistant to breakdown by enzymes

Bupivacaine (Marcaine):

- used for prolonged analgesia and in spinal anesthesia.

Table 14: Comparative pharmacology of commonly used local anesthetics
(Cited in H. R. Adams, 8th Ed.)

Classification	Potency*	Onset of action	Duration of action (min)	pK_a	Fraction nonionized (%) pH = 7.4	Protein binding (%)	Lipid solubility
Esters							
Procaine	1	Slow	45–60	8.9	3	6	0.6
Chloroprocaine	3	Rapid	30–45	8.7	5	—	—
Tetracaine	8	Slow	60–180	8.5	7	76	80
Amides							
Lidocaine	2	Rapid	60–120	7.9	25	70	2.9
Mepivacaine	1.5	Intermediate	90–180	7.6	39	77	1
Bupivacaine	8	Intermediate	180–480	8.1	15	95	28
Etidocaine	8	Slow	240–280	7.7	33	94	141
Prilocaine	1.8	Slow	60–120	7.9	24	55	0.9
Ropivacaine	~8	Intermediate	Similar to bupivacaine	8.1	Similar to bupivacaine	94	Between mepivacaine and bupivacaine

IV. AUTACOIDS (LOCAL HORMONES)

- **Histamine**
- **Serotonin**
- **Angiotensin**
- **Plasma kinins**
- **Substance P**
- **Eicosanoids**
- **Prostaglandins**
- **Prostacyclines & Thromboxane A_2**
- **Platelet activating factor**

BY: HOWAIDA M. EL-KHOLY, PhD

The name AUTACOIDS comes form the two Greek name "Autos" that means self and "akos" that means remedy or chemical. They are chemicals produced by some tissues (not specified) and circulate in the blood to produce their effects.

Members of autacoids

Histamine, seratonin, angiotensin, kinins, substance P, eicosanoids, platelet activating factor and interleukins.

I. HISTAMINE

Sources:

First histamine was thought to be just a bacterial byproduct that have effects similar to ergot alkaloids, but later it was found that it is produced in the animal tissue upon cellular injury. In the body, it is

synthesized through the decarboxylation of the amino acid L-Histidine by the enzyme hisitdine decarboxylase enzyme (Fig. 27).

Fig. 27: Synthesis of histamine

The highest concentration of histamine is stored in the mast cells and basophils. It is present in the highest concentration in the GIT, lungs and skin and in moderate levels in the brain where it functions as a neurotransmitter. The histamine in the GIT is not absorbed due to the bacterial docoposition and the high concentration of the acetylating enzyme in the gut cells. The mast cells and basophils contain also histidine docarboxylase for production of histamine and histaminase enzyme for breakdown of the excess histamine.

External histamine given orally is not absorbed and is broken down in the gut by the digestive enzymes and the metabolizing enzymes, however it is rapidly absorbed if given IM or SC.

Release:

Histamine release takes two main steps the first is the liberation of the histamine-protein granules from the cells and the second is the chemical liberation of histamine from the protein binding. There are some factors that cause release of histamine which are:

1. Proteolytic enzymes that comes out of the cell due to any cell damage as in case of radiation, thermal exposure and physical abrasion.
2. Drugs and chemicals: some drugs have the ability to replace histamine in its storage house by competing it on its binding protein and they liberate histamine without the need to the cell damage such as morphine, d-tubocurarine and trimetaphan.
3. Hypersensitivity and anaphylaxis: the precipitation of Ag-Ab complex in the body leads to cellular injury and the release of histamine.
4. Some poisons and venoms as poison IV and ant and bee venoms.

Histamine receptors:

It was believed that histamine has H_1, H_2 and H_3 receptors but recently in 2001 it was discovered that there is H_4. The H_1 is distributed in the plane muscle in the GIT, respiratory system, blood vessels and uterus. The H_2 is in the parietal cells of the stomach H_3 is in the CNS and some is thought to be in the peripheral nervous system that is responsible for the itching the painful sensation and that in the brain is thought to act as neurotransmitter that inhibit the presynaptic inhibitory transmitter. H_4 receptor is thought to be present in the bone marrow.

Pharmacological effects:

Stimulation of H_1 receptors leads to spasmodic contraction of the smooth muscle of the GIT, bronchi, uterus and the large blood vessels and dilation of the small arterioles and capillaries increasing of the

capillary permeability. The experimental injection of histamine SC leads to the known phenomenon flush, flare and wheel (red, edematous and circle corregate).

Stimulation of H_2 receptors leads to increase in the HCl production in the stomach.

The H_3 receptors stimulation leads to inhibition of the presynaptic inhibitory transmitter and increasing the chance for the stimulatory transmitter to work better dopamine and adrenaline.

The presence of H_4 receptors in the bone marrow have made it be believed to be responsible for some ways of chemotaxis of some of the leukocytes.

Ways of antagonizing the effects of histamine: The effects of histamine can be antagonized by:

1. Use of adrenaline can oppose the H_1 receptor stimulation and it is considered a pharmacological antidote.
2. Using antihistaminic drugs (H_1 antagonists)
3. Using H_2 blockers in case of gastric hyperacidity.
4. Desensitizing the tissue by injecting small doses of histamine to decrease the response to the histamine.
5. Adrenal steroids decrease the Ag-Ab reactions that lead to the cellular injury and release of more histamine

Deactivation: The function of histamine is terminated through one of the following processes.

1. N-Methylation at the NH place by the N-methyle transferase enzyme.
2. Oxidation by the diamine oxidase enzyme.
3. Acetylation by the bacterial acetylating enzyme in the GIT bacteria.
4. Histaminopexy by binding to a specific protein in the plasma.

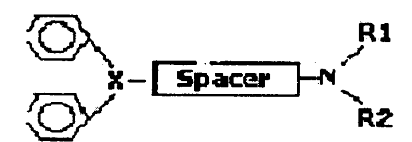
Histamine antagonists:

They are the substances that inhibit the release of histamine from its stores or inhibit its binding to its receptors. Although the term antihistmines means antagonist for the histamine in all of its receptors but classically they are known as H_1 receptors antagonists.

H_1 Blockers:

The H_1 antagonists are classified according to the nature of the molecule at the place of X in the general chemical formula (Fig. 28)

Fig. 28: general formula of antihistamine



a. Ethanolamines where X=O eg. Diphenhydramine and dimenhydrinate.
b. Ethelene-diamines where X=N eg. Tripelennamine, antazoline and mepyramine
c. Alkylamines where X=C eg. Chlorpheniramine
d. Piprazines where X=N as part of piprazine ring eg. Cyclizine and chlorcyclizine
e. Phenothiazines where X=N as part of phenothiazine group as promethazine
f. Piperidines: this group does not belong the general chemical formula above and they include terfenadene and astemizole.

Pharmacological actions of H_1 blockers:

CNS: Most of H_1 blockers have sedative effects, central antiemetics, local anesthetic and antiparkinsonism.

Autonomic NS: some are having anticholinergic effects that cause dry mouth after use like the groups ethanoleamines and ethylendiamines. Some are having antiadrenergic and some have adrenergic action.

Heart: most of them have quinidine-like action.

Therapeutic Uses of H_1 blockers:

1. Allergy and hypersensitivity.
2. Cardiac arrhythmias.
3. Prophylactic in motion sickness.
4. Prevention of vomiting in pregnant women.

Side effects:

Although H_1 blockers are antiallergic drugs some may cause allergic reaction after topical application. Some may cause suppression of the heart. In high doses they may cause excitement and hallucination. And the most prominent side effect is the sedation for most of the H1 blockers that is manifested in drowsiness and sleeping sensation.

H_2 Blockers:

They have a selective H_2 antagonizing effect in the parietal cells of the stomach. From that group are cimetidine, ranitidine and famotidine. This group of drugs are used mainly in case of peptic ulcers to decrease the secretion of HCl in conjunction with antibiotics and stomach protectants like sacralfate.

II. SEROTONIN

Serotonin **(5-hydroxytryptamine, or 5-HT)** is a monoamineT neurotransmitter synthesized in serotonergic neurons in the central nervous system (CNS) and enterochromaffin cells in the gastrointestinal tract of animals including humans. Serotonin is also found in many mushrooms and plants, including fruits and vegetables.

Fig. 29: Serotonin

Serotonin is synthesized in the animal body (mainly the enterochromaffin cells and the brain) from the amino acid tryptophane after its hydroxylation into 5-hydroxytryptophane then its decarboxylation into serotoin (5-hydroxytryptamine). After its synthesis 90% of it is stored in the enterochromaffin cells in the GIT and the rest in the brain and platelets. Serotonin is degraded by the metabolising enzyme monoamine oxidase.

5-HT receptors:

These are 5-HT_1 and 5-HT_2, the brain has both kinds and the smooth muscle and platelets have the second kind only. In the CNS the 5-HT_1 is presynaptic and inhibit the release of adrenaline and 5-HT secretion and the 5-HT_2 is postsynaptic and its stimulation leads CNS excitement, sleeping disturbances and sometimes mood disorders and depression. The 5-HT_2 stimulation causes smooth muscle contratcion and platelet aggregation.

Roles of serotonin:

1. CNS: acts as a neurotransmitter and the disturbance in metabolism leads schizphrania and depression and it plays a role in the regulation of body temperature.
2. GIT: involved in the peristaltic movements.
3. Cardiovascular: it causes the platelet aggregation in case of bleeding and it has known for its triphasic response on the blood pressure. First it causes rapid drop in the blood pressure

accompanied by paradoxical bradycardia followed by a short period of high blood pressure then the last phase of low one.

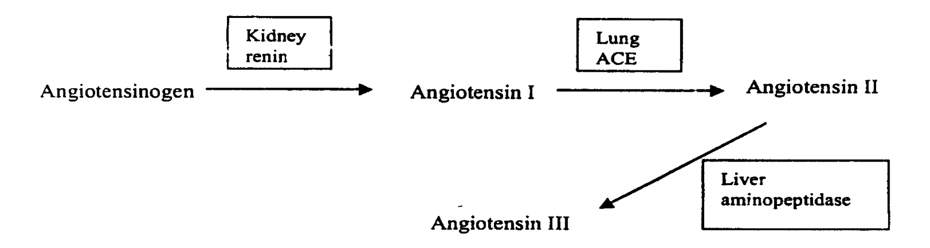
Antiserotonin drugs:

The 5-HT antagonists are used clinically in case of disturbances in the metabolism of serotonin. These are methysergide that is used in case of mild cases of migraine and carcinoid syndrome and the other one is cyproheptadine used in case of allergy, as a growth stimulant and to improve the appetite in children.

III. ANGIOTENSIN (HYPERTENSIN)

Story:

A polypeptide that is present naturally inactive in the plasma in the form of angiotensinogen. The renin enzyme produced by the kidney convert angiotensinogen into the inert angiotensin I then the angiotensin converting enzyme (ACE) that is produced by the lung convert the angiotensin I into the active angiotensin II and then the liver amino-peptidase convert the angiotensin II into the active angiotensin III.



Angiotensin-renin system plays an important role in the regulation of the blood pressure. The baroceptors in the kidney sense the pressure level and controls the production of rennin in the kidneys.

Fig. 30: angiotensin-renin-aldosteron system

Pharmacological actions:

1. Cardiovascular: is a strong hypertensive agent produces its action by direct vasoconstriction and it is 40 times stronger than noradrenaline.

2. Sympathetic: inhances the release of its neurotransmitter noadrenaline and inhibits its uptake that prolongs its time of action.

3. Adrenal cortex: stimulates the secretion and release of aldosterone.

4. Smooth muscles: strong spasmogenic for the intestine, urogenital and bronchial muscles.

Uses: in case of sever hypotension

Antagonism of renin-angiotensin system:

1. inhibition of renin release by methyldopa or propranolol.
2. inhibition of ACE by enalapril
3. blocking of angiotensin II receptors by saralasin.

IV. PLASMA KININS (BRADYKININ AND KALIDIN)

They are plasma polypeptides that are synthesized from the plasma α_2 globulin by the effect of the enzyme kallikrein.

Pharmacological actions of bradykinin:

1. arteriolar vasodilation that is about 10 times the histamine's.
2. increase in heart rate and cardiac output due to direct inotropic and chronotropic action and as a reflex for the fall in the blood pressure.
3. slow stimulation of the smooth muscle of the GIT, bronchi and uterus.
4. increase in capillary permeability that leads to edema.

Clinical role of bradykinins:

1. inflammation: responsible for the redness, pain sensation and edema.
2. anaphylaxis: responsible for some hypotension in cases of anaphylaxis.

3. predominant mediator in case of arthritis and acute pancreatitis and certain carcinoid tumours.

Plasma kinins antagonists: it was found that salicylates and protenin (a protein extracted from bovine tissues) have an inhibiting actions for the enzyme kalikrein and they are used in case of severe inflammation like acute pancreatitis.

V. SUBSTANCE P

Plasma polypeptide extracted from the brain. It has a spasmogenic action and is considered a central and peripheral neurotransmitter and it plays a role in the peristalsis.

VI. EICOSANOIDS

Eicosanoids are signaling molecules derived from omega-3 (ω-3) or omega-6 (ω-6) fats. They exert complex control over many bodily systems, especially in inflammation, immunity and as messengers in the central nervous system. The networks of controls that depend upon eicosanoids are among the most complex in the body. There are four families of eicosanoids—the prostaglandins, prostacyclins, the thromboxanes and the leukotrienes.

VII. PROSTAGLANDINS

Prostaglandins were first discovered and isolated from human semen in the 1930s by Ulf von Euler of Sweden. Thinking they had come from the prostate gland, he named them prostaglandins. It has since been determined that they exist and are synthesized in virtually every cell of

the body. Prostaglandins, are like hormones in that they act as chemical messengers, but do not move to other sites, but work right within the cells where they are synthesized.

Functions of Prostaglandins:

1. Activation of the inflammatory response, production of pain, and fever. When tissues are damaged, white blood cells flood to the site to try to minimize tissue destruction. Prostaglandins are produced as a result.

2. Blood clots form when a blood vessel is damaged. A type of prostaglandin called thromboxane stimulates constriction and clotting of platelets. Conversely, PGI_2, is produced to have the opposite effect on the walls of blood vessels where clots should not be forming.

3. Certain prostaglandins are involved with the induction of labor and other reproductive processes. PGE2 causes uterine contractions and has been used to induce labor.

4. Prostaglandins are involved in several other organs such as the gastrointestinal tract (inhibit acid synthesis and increase secretion of protective mucus), increase blood flow in kidneys, and leukotriens promote constriction of bronchi associated with asthma.

PGD_2	Promotion of sleep
PGE_2	Smooth muscle contraction; inducing pain, heat, fever; bronchoconstriction
$PGF_{2\alpha}$	Uterine contraction
PGI_2	Inhibition of platelet aggregation; vasodilation; embryo implantation

Clinical application of prostaglandins:

1. peripheral vascular disorder.
2. peptic ulcer.
3. induction of birth and abortion.

Prostaglandins antagonists: they act by interfering with the cyclo-oxygenase enzyme needed for the synthesis of prostaglandins. They include adrenal steroids, non steroidal anti-inflammatory drugs and the highly unsaturated fatty acids.

VIII. PROSTACYCLINES AND THROMBOXANE A_2

These two substances work oppositely to each other. Thromboxane A_2 is needed for vasoconstriction and platelet aggregation and is present

deep in the vascular tissue. While prostacycline is vasodilator and prevents platelet aggregation and it is present superficially in the vascular tissue.

IX. PLATELET ACTIVATING FACTOR (PAF)

It has a spasmogenic action on the bronchial smooth muscle and the GIT and is an important mediator in case of inflammation as it causes the vasoconstriction, platelet aggregation, leukocyte chemotaxic and stimulation of the synthesis of prostaglandins. Antagonists of PAF are useful in case of inflammation and bronchial asthma.

V. DRUGS ACTING ON THE CARDIOVASCULAR SYSTEM

- Cardiac stimulants
- Cardiac tonics
- Antiarrhythmic drugs
- Hypertensive and antihypertensive drugs
- Antianaemic drugs
- Coagulant and anticoagulant drugs.

BY: MOSSAD G. A. EL-SAYED, PhD
PROFESSOR OF PHARMACOLOGY

This system has been divided into 3 parts:—

1. Heart. 2. Peripheral vascular system. 3. Blood.

1. HEART

The drugs acting on the heart are classified according to its action into:

A. Cardiac stimulants., B. Cardiac tonics., C. Antiarrhythmics.

A. CARDIAC STIMULANTS

These are the drugs which increase the heart rate and contractile power of the cardiac muscles. These drugs produce a rapid and transient stimulant effects. They are classified according to mode of action into:-

1- Sympathomimetics:

As adrenaline, isoprenaline, amphetamine and metaraminol. Adrenaline is used in case of acute heart failure associated with anaesthesia but not in chloroform or cyclopropane. Administration may be by the i.v. or directly into the heart. The action of adrenaline as a cardiac stimulant is very short. β Stimulants are used in maintaining heart rate during heart block in man. Dose of adrenaline: 0.1 — 0.3 ml. of 1 : 1000 solution.

2. Parasympatholytics:

Atropine and hyoscine increase the heart rate due to the vagal depressant action but they are not commonly used in veterinary practice as cardiac stimulant for their side effects. It is given before the anaesthetics to stimulate the heart and respiratory centers as well as decrease the bronchial secretion.

3. Cardiac muscle stimulants:

As caffeine and theobromine. They stimulate the cardiac muscle directly and vasomotor as well as the vagal center. In general, the increased muscular power due to the direct action causes an increase in ventricular output but the heart rate may be not increase. Theophylline is less active than caffeine as compared to their cardiovascular effects. Aminophylline is more effective now as cardiac stimulant and used for treatment of cardiac insufficiency.

Dose: 2 - 5 g (large animals, 50 - 100 mg (small animals).

4. Reflex stimulants:

When camphor and ether are injected S/C, they produce local irritation and reflexly stimulate the heart as well as respiration Aromatic spirit of ammonia produces also cardiac stimulation reflexly. It is probable that these reflexes originating in the nose, mouth and pharynx are more powerful than those originating in the stomach.

Aromatic spirit of ammonia: 0.6 - 4 ml in dogs.

Therapeutic use of the cardiac stimulant: They are used in case of cardiac depression or faint.

B. CARDIAC TONICS

These are the drugs which stimulate or improve the functional activity of the diseased heart. Their effect is slow but their duration is prolonged. The cardiac tonics of veterinary importance are those cardiac glycosides which derived from the digitalis, strophanthus and squill plants.

Cardiac glycosides

1. Digitalis (Foxglove)

The leaves and seeds of *Digitalis purpura* and *Digitalis lanata* containing the glycosides, digitoxin, gitoxin and digitalin. Digitoxin is the more powerfull cardiac tonics and digitalin is the least, while the gitoxin is intermediate. Digitoxin appear in the urine after 50 days of single dose while gitoxin is excreted within 2 days.

Digitalin is rapidly excreted (Fig. 31)

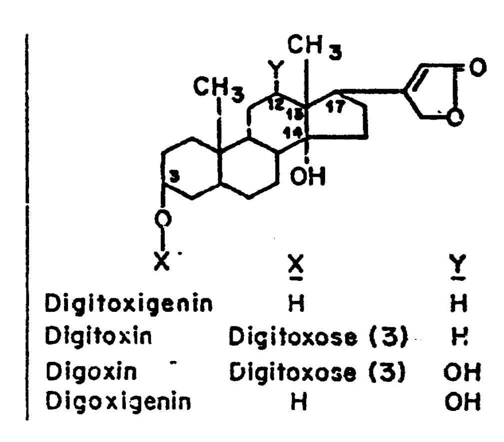


Fig. 31: Structure arrangement of digoxin and digitoxin

Pharmacological actions:

1. On the heart:

a) Digitalis increases the force of systolic contraction by direct effect on the myocardium.

b) It increases the cardiac output in congestive heart failure. It decreases the heart rate by a reflex vagal stimulation through the sensitization of the carotid baroceptors. As a result, it slows the S.A. node and delays the A.V. conduction.

c) It normalizes the cardiac excitability in case of cardiac failure.

d) It shortens the refractory period of the auricles and ventricles, while of the A.V. node and bundle of His is prolonged.

e) The ECG picture is changed including a diminished or inverted T, depressed RST, prolonged P-R and shortened Q-T interval.

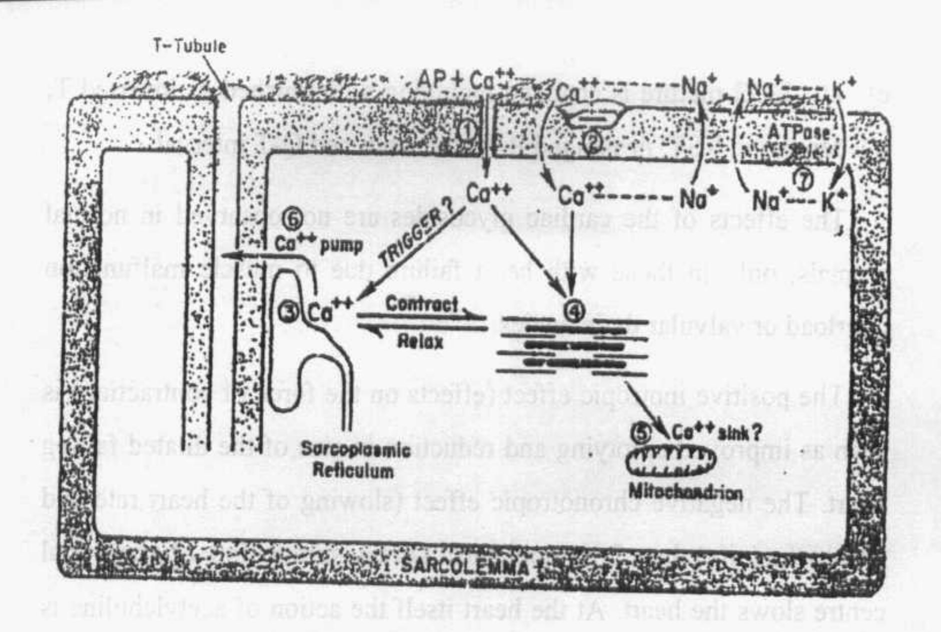
The effects of the cardiac glycosides are not observed in normal animals, only in those with heart failure due to muscle malfunction overload or valvular deficiencies.

The positive inotropic effect (effects on the force of contraction) is seen as improved emptying and reduction in size of the dilated failing heart. The negative chronotropic effect (slowing of the heart rate and its rhythmicity) has 2 components. Direct stimulation of the vagal centre slows the heart. At the heart itself the action of acetyleholine is potentiated and that of sympathetic mediators is inhibited.

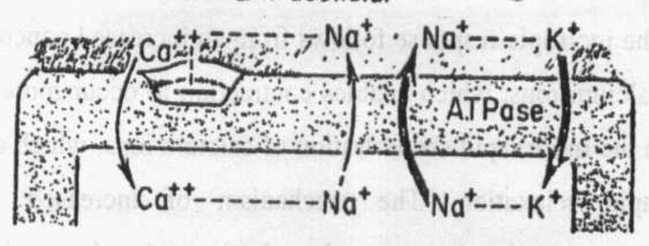
Mode of action:

The inotropic response follows from an increased concentration of free calcium ions, which enables contraction to occur more rapidly and form the more rapid sequestration of calcium ions, which allows a more rapid relaxation. The mechanism of increased calcium concentration remains unknown, but does not involve endogenous catecholamines.

The site of action of cardiac glycosides is the plasmalemma. The ability of glycosides to decrease the intracellular K^+ concentrations lies in their ability to bind to Mag-dependent transport ATP as in the membrane. This is the active mechanism which pumps Na^+ out of the cell and K^+ in, but its inhibition is believed responsible for digitalis toxicity.



A. NORMAL



B. AFTER DIGITALIS

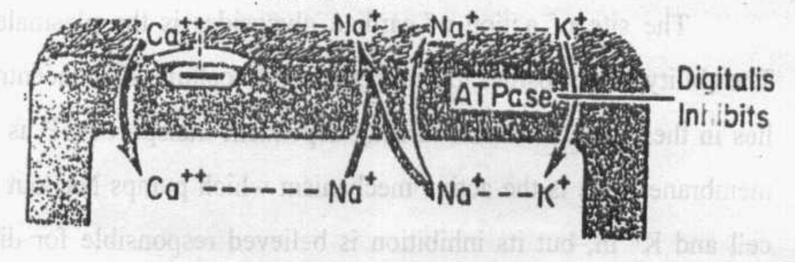


Fig. (32): Mechanism of action of digitalis.

It is suggested that intra-cellular Na^+ accumulation displaces sequestered Ca^{++}, or that the digitalis—impeded Na/K ATPase pumps Ca^{++} into the cell and K^+ out. Binding of glycosides to phosphory lated ATPase in the pre- K^+ -uptake part of the transport cycle would both increase the labilization of Ca^+ and inhibit the inwards pumping of K^+ (Fig. 32).

2. On blood pressure:

The therapeutic dose of digitalis does not produce any change in B.P. in normal animals but in case of congested heart failure, digitalis increase the B.P. due to increase in force of contraction. Toxic dose produce a raise in B.P. due to direct vasoconstrictor effect on the muscle of the blood vessels. Also digitalis stimulates centrally the vasomotor centre.

3. On coronary circulation:

The therapeutic dose of digitalis has no effect.

4. On the medulla:

The therapeutic dose stimulates the vagal centre, but toxic dose stimulates the vasomotor, respiratory and vomiting centers.

5. On the kidney:

Digitalis is secondary diuretic by increasing the cardiac output, increase in glomerular filtration and decrease aldosterone secretion (which decreases the Na reabsorption). The diuretic action of digitalis is augmented by mercurial diuretics; but do not combine digitalis and

mercurial diuretics because the diuresis produced by mercurial diuretics will concentrate the digitalis in the body and leads to toxicity.

Toxicity:

1. Nervous symptoms: as headache, convulsions, fatigue and muscular weakness.
2. Gastro-intestinal symptoms: as nausea and vomition as well as diarrhoea.
3. Cardiac symptoms: as arrhythmia and fibrillation due to direct action on the cardiac muscle and depression of the heart as a result of excessive stimulation.

Treatment:

1. Stop further administration of digitalis.
2. Remove the stomach and intestinal contents by emetics or purgatives as caster oil.
3. Give atropine to limit vagal stimulation.

Therapeutic uses of digitalis:

1. For the treatment of congested heart failure due to valvular diseases in man and dogs.
2. In case of auricular muscular flutter which is a sudden increase in heart rate/min, and although the beats are very rapid yet they are very regular.

Digitalis is rarely used in cats because it produces vomition.

It is not used in horse or cattle because the animals becomes of no benefit and usually killed or slaughtered.

Dose:

- In ruminants, digitalis must be given by i.v. or i.m. because it is destroyed in the rumen.
- Tr. is given orally, 8 - 15 cc (horse), 0.3 — 1 cc (dogs).
- i.m. injection : 0.1- 1 mg in dogs for few days and then 0.025 mg as maintainance dose.

2. Strophanthus:

Its active principle is called strophanthin. It has similar actions to those of digitalis but:

a) Its Tr. causes less irritation to the stomach.

b) The absorption and excretion are more rapid and less cumulative.

c) It has strong diuretic effect because it has no vasoconstrictor effect.

d) The Tr. is given orally, but the glycoside is given by i.v. route.

10 - 12 mg in horse and cattle, 0.25- 1 mg in dogs.

3. Squill (Scilla):

Its active principles is scillarin:

1) It has a mild cardiac effect.

2) It is more irritant to the gastric mucosa and reflexly stimulates the bronchial secretion, so Tr. scilla is used in cough mixture.

3) It is the most pow rful diuretic (because it irritates the renal cells during excretion.

C. ANTIARRHYTHMIC DRUGS

Introduction:

1- The **sinus node** normally controls the heart rate and rhythm.

2- **Causes of abnormal heart rhythms** include:

a. Disturbances in sinus node function.

b. Altered automaticity of other cardiac fibers.

c. Abnormal conduction anywhere in the heart.

d. Combinations of these factors.

Drugs used for tachyarrhythmias

TABLE (15) Classification of Antiarrhythmic Drugs

Class	Agents	Mechanism of Action	ECG Effects
I		Decrease fast inward Na^+ current; stabilize membrane by decreasing conductivity, excitability, and automaticity	
A	Quinidine Procainamide Disopyramide	Moderately decrease conductivity, increase action potential duration	Prolonged QRS and QT intervals
B	Lidocaine Phenytoin Tocainide Mexiletine	Decrease action potential duration with little change in conductivity	Unchanged QRS and QT intervals
C	Flecainide Encainide Propafenone	Markedly decrease conductivity without changing action potential duration	
II	Propranolol Atenolol Esmolol Metoprolol Nadolol Pindolol	β-Adrenergic blockade (reduce sympathetic stimulation with no direct effects on myocardium at clinical dosages)	
III	Bretylium Amiodarone Sotalol	Selectively prolong action potential duration and refractory period; antiadrenergic effects	Prolonged QT intervals
IV	Verapamil Diltiazem	Decrease slow inward Ca^{2+} current (greatest effects on S-A and A-V nodes)	

A-V = atrioventricular; Ca^{2+} = calcium; ECG = electrocardiogram; Na^+ = sodium; S-A = sinoatrial.

1- Class I agents

They include drugs with local anesthetic actions.

a. Preparations:

(1) **Class IA** drugs include quinidine, procainamide, and disopyramide.

(2) **Class IB** drugs include lidocaine, phenytoin (Dilantin)®, tocainide, and mexiletine.

(3) **Class IC** drugs include flecainide, encainide, and propafenone.

b. Mechanisms of action

(1) Class I agents have **local anesthetic effects,** which alter the automaticity, excitability, conduction, and refractoriness of the cardiac membranes.

(2) Some Class I agents (e.g., quinidine, procainamide) also have **indirect autonomic effects.**

(3) Most Class I agents are dependent on extracellular potassium concentration for their effects.

c. Pharmacologic effects

(1) Class IA drugs

a) **Procainamide** and **quinidine** depress automaticity and conduction velocity and prolong the effective refractory period. These effects result from both the electrophysiologic (direct) and vagolytic (indirect) actions of the drugs. At low doses, quinidine's vagolytic

effects may cause increases in the sinus rate or the ventricular response rate to atrial fibrillation by antagonizing the drug's direct effects.

(b) **Disopyramide** is similar to quinidine and procainamide electrophysiologically but has significant depressive effects on the canine myocardium. It also has a half-life of less than 2 hours in dogs; thus, it is not used clinically.

(2) Class IB drugs

(a) Lidocaine

(i) Lidocaine suppresses automaticity in both normal Purkinje fibers and diseased myocardial tissue, slows conduction, and reduces the supernormal period. Its effects are enhanced in diseased or hypoxic cardiac cells.

(ii) Lidocaine produces minimal hemodynamic effects and little to no depression of contractility at therapeutic doses when given slowly intravenously; however, hypotension has been associated with toxic levels.

(iii) Lidocaine has little effect on sinus rate, A-V conduction rate, and refractoriness.

(b) **Tocainide** is similar to lidocaine in its electrophysiologic and hemodynamic properties.

(c) **Phenytoin** is similar to lidocaine; however, it also has some slow calcium channel inhibitory and central nervous system (CNS)

effects that may contribute to its effectiveness against arrhythmias induced by the digitalis glycosides.

(d) **Mexiletine** is similar to lidocaine in its electrophysiologic, hemodynamic, and antiarrhythmic properties.

(3) **Class IC drugs: Flecainide** and **encainide** markedly reduce cardiac conduction velocity and may depress automaticity in the sinus node and specialized conducting tissues at high dosages.

d. Therapeutic use: Class-I antiarrhythmic agents are used Primarily for frequent ventricular premature contractions and ventricular tachycardia.

(1) **Class IA drugs: Procainamide and quinidine** may also be effective for atrial premature depolarizations and tachycardias.

(a) Quinidine may cause conversion to sinus rhythm in horses, cats, and large dogs with recent onset of atrial fibrillation and clinically normal ventricular function.

(b) Procainamide is less effective than quinidine for atrial arrhythmiais, and it is not effective in converting chronic atrial fibrillation to sinus rhythm.

(2) **Class IB drugs**

(a) **Lidocaine** is usually the intravenous ventricular antiarrhythmic agent of choice in the dog, but it is generally ineffective for supraventricular arrhythmias.

(b) Phenytoin is used only in dogs for the therapy of digitalis glycoside-induced ventricular arrhythmias that are not responsive to lidocaine. **Phenytoin is not used in cats or horses.**

(3) **Class IC drugs: Flecainide** and **encainide** have been associated with an increased mortality rate in humans; thus, they are used only with caution and for life-threatening ventricular arrhythmias refractory to more conventional therapy.

e. Contraindications

(1) All Class I agents are contraindicated in the presence of complete heart block.

(2) Class I agents should be used cautiously in patients with sinus bradycardia, sick sinus syndrome, and first- or second-degree A-V nodal block.

f. Drug interactions

(1) **Positive interactions.** Concurrent use of a class I drug and a drug of another class (or even subclass) may increase antiarrhythmic efficacy in cases refractory to a single agent.

(2) **Negative interactions**

(a) Class IA drugs

(i) Cimetidine blocks renal tubular secretion of procainamide and predisposes the patient to

quinidine toxicity by slowing elimination of quinidine.

(ii) Quinidine can precipitate digoxin toxicity when both drugs are used together, because it displaces digoxin from skeletal muscle binding sites and decreases digoxin's renal clearance.

(iii) Anticonvulsants and other drugs that induce hepatic microsomal enzymes can speed the metabolism of quinidine so that an increased dosage may be needed.

(b) Class IB drugs

(i) Propranolol, cimetidine, and other drugs that decrease liver blood flow slow the metabolism of lidocaine. Reduced hepatic blood flow associated with heart failure can also predispose the patient to toxicity.

(ii) Cimetidine, chloramphenicol, and other drugs that inhibit microsomal enzymes can result in toxic serum concentrations of phenytoin.

2. Class II agents

It includes β-blockers (see Table 15).

a. Preparations

Propranolol (Inderal)® has been used most widely in veterinary medicine. Atenolol and other β-blockers are also used now.

b. Mechanism of action:

β-Adrenergic antagonists act by inhibiting catecholamine effects on the heart.

c. Pharmacologic effects:

Class II agents slow the heart rate and A-V conduction velocity and reduce contractility, myocardial oxygen consumption, and systemic vascular resistance.

(1) Class II agents block sympathetic effects; therefore, pharmacologic effects are proportional to existing sympathetic tone.

(2) Although β-blockers have a minimal negative inotropic effect in normal animals, in those with severe underlying myocardial disease that depend on increased sympathetic drive to maintain cardiac output, they can depress cardiac contractility, conduction, and heart rate.

d. Therapeutic uses:

(1) β-Blockers are indicated for the treatment of **supraventricular tachyarrhythmias,** such as paroxysmal atrial tachycardia and frequent atrial premature complexes. They may also be helpful for some ventricular tachyarrhythmias.

(a) In cats, β-blockers are the drug of choice for both supraventricular and ventricular tachyarrhythmias.

(b) Esmolol, a newer agent with β_1 selectivity and a half-life of less than 10 minutes, is potentially useful for short-term treatment of acute tachyarrhythmias and hypertrophic obstructive cardiomyopathy.

(2) β-blockers slow the ventricular response rate in **atrial fibrillation.** They are often used in combination with digoxin.

(3) β-Blockers are also used to decrease heart rate and myocardial oxygen demand in hypertension, **hypertrophic cardiomyopathy,** and other causes of myocardial hypertrophy.

e. Drug interactions:

(1) β-Blockers enhance the depression of A-V conduction produced by the digitalis glycosides, class I antiarrhythmic drugs, arid calcium channel blockers. The simultaneous use of a β-blocker and a calcium channel blocker is not recommended and can lead to marked decreases in heart rate and myocardial contractility.

(2) β-Blockers may decrease liver blood flow, leading to reduced elimination of drugs that are highly dependent on liver blood flow for clearance (e.g., lidocaine and phenytoin).

3. Class III agents

They prolong action potentials.

a. Preparations:

(1) Bretylium tosylate

(2) Amiodarone

(3) Sotalol

b. Mechanism of action:

Class III agents prolong the cardiac action potential duration and the effective refractory period without decreasing conduction velocity.

c. Pharmacologic effects:

(1) Bretylium causes an initial catecholamine release, followed by a longer period where norepinephrine release is inhibited. Intravenous administration produces a transient increase, followed by prolonged decrease, in sinus rate, A-V conduction velocity, vascular resistance, and arterial blood pressure. The antifibrillatory effects of bretylium may be delayed 4-6 hours after administration.

(2) Amiodarone in therapeutic dosages slows the sinus rate, decreases the A-V conduction velocity, and causes minimal depression of myocardial contractility and blood pressure.

(3) Sotalol is a nonselective β-blocker with primarily class III activity; thus it prolongs repolarization time and refractoriness.

d. Therapeutic uses

(1) Class III agents are most effective for suppressing re-entrant arrhythmias and preventing ventricular fibrillation.

(2) Bretylium, amiodarone, and d-sotalol may he indicated for the treatment of life-threatening ventricular arrhythmias that are not responsive to conventional therapy and for other patients at risk for developing ventricular fibrillation. They are not indicated for initial therapy of ventricular arrhythmias.

e. Drug interactions:

Amiodarone increases the serum concentration of digoxin quinidine, procainamide, phenytoin, and theophylline.

4. Class IV agents

They are calcium channel blockers.

a. Preparations:

(1) Diltiazem (Cardizem)®

(2) Verapamil (Calan. Isoptin)®

b. Mechanisms of action:

Class IV drugs reduce calcium influx by blocking the slow inward calcium current. Tissues dependent on the slow inward calcium current (e.g., the sinus and A-V nodes) are most affected.

c. Pharmacologic effects:

Calcium channel blockers cause dose-related slowing of sinus rate and A-V conduction. As a group, they cause coronary and systemic vasodilation, enhanced myocardial relaxation, and

reduced cardiac contractility. Some calcium channel blockers have antiarrhythmic effects.

(1) Diltiazem causes potent coronary and mild peripheral vasodilation. It has less negative inotropic effect than verapamil.

(2) Verapamil has significant negative inotropic and some vasodilating effects that can cause serious decompensation, hypotension, and even death if underlying myocardial disease is present.

d. Therapeutic uses:

(1) Diltiazem and verapamil are effective against re-entrant supraventricular and atrial tachycardias.

(2) Diltiazem is also used to slow the ventricular response rate in atrial fibrillation, usually in combination with digoxin.

Drugs used for bradyarrhythmias

1. Anticholinergic (vagolytic) drugs

a. Preparations:

(1) Atropine

(2) Glycopyrrolate

(3) Propantheline bromide

b. Mechanism of action:

Anticholinergic drugs competitively antagonize the action of acetylcholine (ACh) at muscarinic receptors.

c. Pharmacologic effects:

(1) An increase in heart rate is the main cardiac effect of anticholinergic drugs. Heart rate effects in dogs last 60—90 minutes with atropine.

(2) Atropine injection may cause a transient centrally mediated worsening of a bradyarrhythmia

d. Therapeutic uses:

(1) Indications for parenteral atropine or glycopyrrolate include bradycardia and A-V block induced by anesthesia, CNS lesions, and other diseases or toxicities.

(2) An atropine response test is often used in (dogs and cats presenting with a bradyarrhythmia to determine the extent of vagal influence.

(3) Propantheline bromide or other oral anticholinergic therapy may he useful in treating sinus bradycardia, sick sinus syndrome, and partial A-V blocks that are responsive to parenteral atropine

2- PERIPHERAL VASCULAR SYSTEM

A. Hypertensive drugs: (vasoconstricutors)

These are the drugs which raise the arterial blood pressure.

They are classified according to the mode of action into:

1) Vasomotor stimulants: as analeptics i.e. nikethmaide.....

2) Adrenergic stimulants: as adrenaline, nor-adrenaline, ephedrine, amphetamine.

3) Smooth muscle stimulants: as ergot alkaloids, vasopressin.

4) Mechanical by i.v. injection of plasma expanders as saline, dextran, whole blood, plasma and serum.

Ergot alkaloids: as ergotoxine, ergotamine and ergometrine. Although they are antagonists to adrenaline, but they rise the blood pressure due to its direct constrictor action on the smooth muscles of the peripheral blood vessels, coronaries and renal blood vessels.

Vasopressin (ADH): It is the posterior pitutary antiduiretic hormone. It rises the blood pressure only by doses in excess of those required for antidiuretic effect. The rise in blood pressure by vasopressin is attributed to the direct action on the vascular smooth muscle.

B. Antihypertensive drugs

Introduction:

1- **Systemic arterial hypertension** has been associated with renal disease, hyperadreno-corticism, and pheochromocytoma in dogs and with renal disease and hyperthyroidism in cats. In some cases, no underlying cause in identified.

2- **Therapy** usually includes dietary salt restriction and management of underlying diseases. Drug therapy is individualized for each patient, usually using one or more of the following agents:-

1. Diuretics

a. **Mechanism of action:** Diuretics may reduce blood pressure by promoting sodium and water excretion.

b. Furosemide is most commonly used, although hydrochlorothiazide may be helpful in nonazotemic dogs.

2. **β-Blockers**

a. **Mechanism of action:** β-Blockers may reduce blood pressure by slowing heart rate, decreasing cardiac contractility, or by other peripheral and central mechanisms.

b. Propranolol and atenolol are used most commonly in animals.

3. **Vasodilators.**

3.1. ACE inhibitors

a. **Mechanism of action:** ACE inhibitors may help control blood pressure by reducing angiogenesis II formation vasodilator kinin degradation, and aldosterone release.

b. In dogs and cats, ACE inhibitors may be used alone, with a diuretic, or with a diuretic and a β-blocker.

3.2. **Hydralazine** and **α-blockers** (e.g. prazosin, phentolamine, phenoxybenzamine) have been tried in some dogs with uncertain success.

4. **Calcium channel blockers** decrease intracellular calcium in vascular smooth muscle, reducing vascular resistance. Some agents also reduce cardiac output by slowing heart rate, decreasing contractility, or both nifedipine and diltiazem may be useful. Recently, amlodipine besylate has produced positive results in hypertensive cats.

5. **Direct vascular smooth muscle relaxants** as pap-paverine, nitrite, theophylline and khellin.

3. DRUGS ACTING ON BLOOD

A. ANAEMIAS AND ANTIANAEMIC DRUGS

Anaemia is a condition which may arise from failure either to make sufficient red corpuscles or to synthesis sufficient haemoglobin. See table (16) for types of anaemias.

1. Iron deficiency or hypochroinic microcytic anaemia:

A deficiency of iron or inability to absorb or utilize it because of the absence of other factors, as copper or cobalt and a deficiency of dietary protein, will both cause a hypochromic anaemia. The main drug for the treatment of microcytic anaemia is one member of the iron compounds:

Table (16): Classification of anaemias.

Morphologic classification		
Size of erythrocyte	Hemoglobin content	Etiologic classification
Macrocytic anemias		
Type I macrocytic	Normochromic	Cobalt deficiency (vitamin B_{12} deficiency) Congenital prophyrinuria
Type II macrocytic	Hypochromic	Transitory condition occurring during the active phase of erythrocytic regeneration following acute blood loss or erythrocyte destruction: (1) spontaneous hemorrhages from hypoprothrombinemia caused by spoiled sweet clover, (2) bacillary hemoglobinuria, (3) leptospirosis, (4) parturient hemoglobinuria, (5) anaplasmosis, (6) piroplasmosis, (7) *Haemobartonella* infection
Normocytic or normochromic anemias		
Normocytic	Normochromic	Subacute and chronic inflammatory diseases Acute blood loss unaccompanied by intense bone marrow response Nephritis with terminal uremia
Normocytic	Hypochromic	Stomach worm infection (excluding *Haemonchus*, which causes blood loss)
or		
Microcytic	Normochromic	Leukemia or other marrow displacements Hypoplastic anemias: (1) bracken fern poisoning, (2) poisoning from soybean meal extracted with trichloroethylene, (3) radiation injury
Microcytic	Hypochromic	Deficiency of iron: (1) chronic blood loss from injury, which does not heal, to vascular bed, (2) heavy infection with blood sucking parasites (*Haemonchus*, lice, ticks, etc.), (3) dietary iron deficiency Defect in utilization of iron stores of body: (1) copper deficiency, (2) molybdenum poisoning

1) **Ferrous sulphate:** It is green crystal or powder with an astringent metalic taste. It was commonly used as intestinal astringent in animals. It is used also as a haematinic. It is better than ferric form because it is well absorbed and less astringent then ferric salts. Ferrous sulphate may be given in combination with copper sulphate.

Dose: 4-15 g (large animals), 100—300mg (small animals).

2) **<u>Reduced iron and iron pyrophosphate</u>:** Oral dosing with reduced iron or iron pyrophosphate has been widely used. They are used in a dose of 0.5 - 1 g daily. This method is expensive.

3) **Iron carbohydrate complexes:** as iron dextran, which must be administered by i.m. route. The absorption is sufficiently rapid from the site of injection.

4) **Ferrous carbonate:** Is used in the form of a pill or tablet as haematinic in small animals.

5) **Ferrous gluconate and succinate:** They are less irritant, less constipating and more absorbed, especially if combined with vitamin B complex. Dose: 0.3 g twice daily to small animals.

6) **Scally preparations:** Iron ammonium citrate, iron strychnine citrate and iron quinine citrate arc less irritant and astringent than ferrous salts. Dose: 0.3 - 0.5 g. orally.

7) **Saccarated iron oxide:** Is given by i.v. injection, in case of animals which are unable to absorb iron.

2. Pernicious, or hyperchromic macrocytic anaemia:

The cause of pernicious anaemia is deficiency of vitamin B_{12} or folic acid. This is called extrinsic factor, which required for its absorption the presence of intrinsic factor. The latter is the specific substance secreted by the normal gastric mucosa.

Clinically, pernicious anaemia is characterized by:

a) Macrocytic anaemia.

b) Achylia gastrica.

Drugs used in pernicious anaemia:

1) Vitanin B_{12} (Cyanocobalamin):

It is synthesized by certain microorganisms occuring in intestine, rumen and soils. It is rich found in the liver, meat, eggs and milk. Vit. B_{12} is better given by i.m. injection. Oral administration needs very large doses and render the therapy expensive. It is given as it is or as liver extract which is rich in the vitamin. The dessicated hog stomach preparation as a substitute for intrinsic factor is also given.

2) **Folic acid** is of value in treating pernicious anaemia.

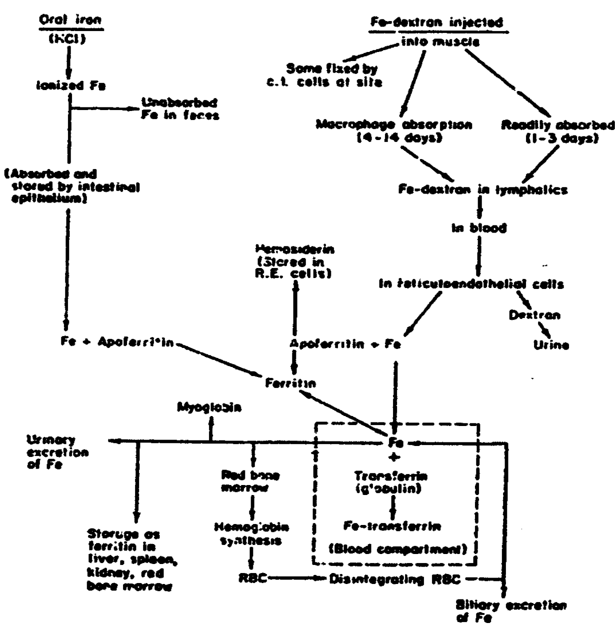


Fig. 33: Iron metabolism

3. Haemorrhagic anaemia

It is treated by blood transfusion or by iron rich diet.

4. Aplastic anaemia

The main cause of aplastic anaemia is depression of the bone marrow by poisons or radioactive substances. The aplastic anaemia is treated by the proper cause.

5. Haemolytic anaemia

It is caused by destruction of R.B.Cs. by bacteria or parasites or toxins. It is treated by preventing the cause.

B. DRUGS ACTING ON BLOOD COAGULATION:

The body is protected against haemorrhage by a reflex vasoconstriction decreasing the amount of blood and by clotting process.

The clotting mechanism involves a chain of reactions ending with the formation of a solid clot from the fluid blood.(Fig. 34).

1. COAGU1ANTS

Coagulant or haemostatics are drugs used to arrest bleeding. They are classified according to their site of action into:

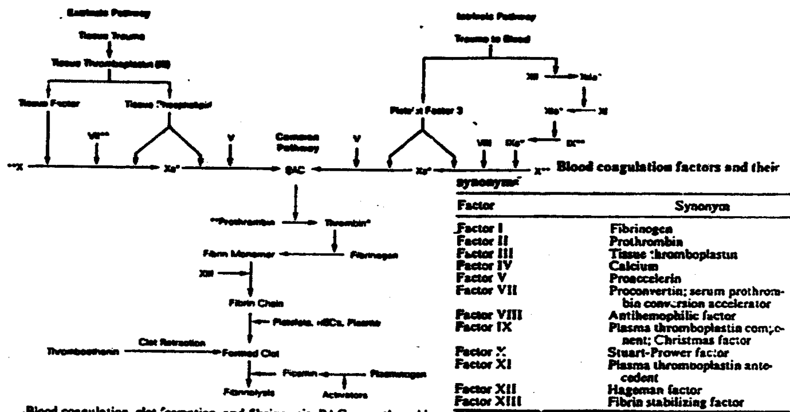
1) Local coagulants:

a) Physical methods:

1. Pressure on the bleeding surface.

2. Application of cold to constrict the bleeding vessels.

3. Heat coagulation.



Blood coagulation factors and their synonyms*

Factor	Synonym
Factor I	Fibrinogen
Factor II	Prothrombin
Factor III	Tissue thromboplastin
Factor IV	Calcium
Factor V	Proaccelerin
Factor VII	Proconvertin; serum prothrombin conversion accelerator
Factor VIII	Antihemophilic factor
Factor IX	Plasma thromboplastin component; Christmas factor
Factor X	Stuart-Prower factor
Factor XI	Plasma thromboplastin antecedent
Factor XII	Hageman factor
Factor XIII	Fibrin stabilizing factor

Blood coagulation, clot formation, and fibrinolysis. PAC = prothrombin activator complex (also referred to as complete thromboplastin, prothrombinase, prothrombinase complex, and intrinsic or extrinsic thromboplastin); a = activated forms of clotting factors; * = factors inhibited by heparin; ** = factors inhibited by coumarin derivatives. Calcium is required in most reactions.

Fig. 34: Blood coagulation, clot formation and fibrinolysis

b) Astringents or protein precipitants: As alum and ferric chloride. and tannic acid.

c) Adrenaline: Local application to the bleeding area a may arrest bleeding. The effect is due to vasoconstriction of the capillaries and other small vessels.

d) 5-Hydroxytryptamine creatinine sulphate: It produces vasoconstriction of the capillaries and small blood vessels. It is physiological haemostatic.

e) Oxidized cellulose, calcium alginate and absorbable gelatin.

2) **Systemic coagulants:**

These are drugs which are used to stop internal haemorrhage:

a) Vitamin K: it is essential for the formation of prothrombin and factor VII in the liver.

b) Calcium: In case of hypocalcaemia.

c) Vitamin C and Rutin: In case of abnormal capillary fragility.

d) Blood transfusion: Can be helpful to supply the factors required for the coagulation.

2- ANTICOAGULANTS

These are substances or drugs which interfere with the coagulation of blood *in vivo* or *in vitro*.

a) The *in vitro* anticoagulants

1) Drugs which precipitate calcium *in vitro*: sodium or pot. Oxalate and sodium fluoride.

2) Drugs which diminish the ionization of calcium but did not precipitate it as sodium citrate. Sodium citrate reacts with ionized calcium to form sodium calcicitrate which is soluble but non-ionizable. *In vitro*, 0.4 % sod. citrate solution delays blood coagulation for about 2 days.

3) Sodium edetate (EDTA): This inhibits blood coagulation by forming on undissociated complex (chelate) with calcium.

b) The *in vivo* or systemic anticoagulants

1) Heparine:

It is a mucopolysaccaride. It is naturaily occuring substance secreted by the mast cells of the liver, lungs, and other tissues.

Heparine as such is not active, but in the body it combines with some factor in the plasma proteins to produce anticoagulant action. In solution, the molecules of heparin carry an electronegative charge to which heparin owes its anticoagulant properties.

Mode of action

1) It interfers with the conversion of prothrombin to thrombin i.e. anti-thromboplastin.
2) It inhibits the conversion of fibrinogen into fibrin by thrombin. i.e. anti-thrombin.
3) It interferes with the clamping of platelets.

Heparin possesses a lipaemia clearing action. The plasma clearing factor is suggested to be a lipolytic enzyme. Heparin is supposed to be act by enhancing the activity of this enzyme.

Heparin is usually administered intravenously as sodium salt and the action is immediate. The duration of action is short because of its rapid inactivation in the liver. It acts *in vivo* and *in vitro*.

Therapeutic uses:

1. Prophylaxis and treatment of thrombo—embolic diseases.

2. As a plasma clearing factor in hyperlipaemic states.

3. For prevention of coagulation in blood samples i.e. *in vitro*.

2) Dicumarol:

This is a naphthoquinone derivatives. It was isolated from spoild sweet clover. It is now prepared synthetically. It is a colorless crystalline substance.

Mode of action:

Dicumarol and other coumarin derivatives inhibit the formation of factor VII and prothrombin by the liver. This action may be due to interference with the hepatic utilization of vitamin K. The effects of this drug upon the blood coagulation appear only after the utilization of the already existing plasma prothrombin. As a result, dicumarol possesses a delayed onset of action. Furthermore, when the drug is stopped there will be a delayed action.

Absorption and fate:

It is readily absorbed from the G.I.T. After absorption, the drug is largely bound to plasma proteins. It is concentrated to a large extent in the liver of the drug is unknown.

Therapeutic uses:

Unlike heparin, it is given by mouth. It is used for the prophylaxis and treatment of thrombo-embolic diseases.

3) **Warfarin sodium**: is an anticoagulant. It competes with vitamin K and blocks formation of prothrombin. It is used as rudenticide as well as in human therapy.

4) **Indanediones:** e.g. phenindione, are structurally related to the coumarines and produce anticoagulants effect in the same manner. They cause kidney damage, sensitivity reactions and leukopenia.

VI. PHARMACOLOGY OF THE DIGESTIVE SYSTEM

- **Preface**
- **Drugs affecting appetite**
- **Drugs affecting stomach**
- **Drugs affecting intestines**
- **Drugs affecting liver**

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PREFACE

- The digestive system is mainly composed of mouth, pharynx, stomach, and intestine (gastrointestinal tract) as well as liver and pancreas.
- Digestive tract differs according to species of animals e.g. some animals have compound stomach (ruminants), others have simple stomach (horse and dog).
- Some animals have well developed vomiting center (pig and dog), while others have no well developed vomiting center (horse and cattle).

DRUGS WHICH AFFECT APPETITE

SIALAGOGUES

Def: These are drugs which increase the secretion of salvia (the volume and fluidity of saliva).

- The aim of sialagogues is to improve the appetite and digestion.
- Salivary gland are supplied by parasympathetic (secretory) and sympathetic nerves.

Classification according to their mechanism of action:

1- **Reflex sialagogues (Bitters or Stomachics):**

Substances which slightly irritate the taste buds on the tongue or/and the sensory nerve ending of gastric mucosa and reflex stimulate the salivary glands to improve salivation.

2- **Direct sialagogues:** They act either by:

   a. Stimulating the parasympathetic nerves (parasympathomimetics); e.g. acetylcholine, carbachol, physostigmine. But not used for this purpose.

   b. Stimulating of the secretary cells of the salivary glands during their excretion; e.g. pot. iodide, sod. salicylate in large doses.

ANTISIALGOGUES

Def: These are drugs which decrease excess secretion of saliva.

Mechanism of Action:

1- Blocking the parasympathetic nerve as atropine, tr. Belladonna.

2- Depressing directly the secretary cells of the salivary glands as by astringents (tannic acid, catechu).

Uses: Antisialagogues are used in case of poisoning by metallic salts, organic phosphorous compounds to check excess saliva secretion.

STOMACHICS (BITTERS)

Def: These are drugs which increase the appetite by increasing salivary and gastric secretions in cases of loss of appetite.

- Their effect is not clear when the appetite is normal.
- There are usually given before meals in form of mixture or electuary.

Classification according to their content into:

1- Simple (Non-aromatic) bitters: They contain only a bitter substance. Most of them are of plant origin e.g.:

(1) Non alkaloidal stomachics as gentian, quassia, calumba.

(2) Alkaloidal stomachics as quinine and strychnine.

* Some simple stomachics are non-vegetables e.g. vinegar, alcohol and alkalines in small doses.

2- Compound (aromatic) bitters: They are plants which contain volatile oils beside their bitter substances e.g. bitter orange peel, lemon peel, cardamon, etc.

They are also used as flavoring agents for their aromatic taste.

DRUGS AFFECTING STOMACH

ANTI-ACIDS

Def: These are drugs which are given orally to neutralize excess gastric acidity. They are used for treatment of:

1- Gastric hyperacidity and gastric ulcer.

2- Ruminal indigestion due to excess carbohydrate fermentation in the rumen where excess lactic acid is formed.

Classification: according to their site of action into:

1- Local antacids:

They are insoluble alkaline salts which are not absorbed acting only on hyperacidity of the stomach.

They are either:

(a) Those do not evolute CO_2 gas when react with gastric acidity such as mag. oxide, mag. Trisilicate and aluminum hydroxide.

(b) Those evolute CO_2 gas such as mag. Carbonate and ca. carbonate. The evolution of CO_2 gas in the stomach may lead to return of hyperacidity after a short period of relief because distention of stomach with CO_2 gas leads to restimulation of acid secretion.

2- Systemic (general) antacids:

They are soluble alkaline salts which are readily absorbed acting on both gastric acidity before their absorption. Those do not evolute CO_2 gas in the stomach such as sod. bicarbonate. After absorption, they render acid urine alkaline acting as urinary alkalinizes.

3- **H_2 receptor blockers:**

They are the drugs which inhibit the stimulatory effect of histamine on H_2 receptors present on gastric glands e.g. cimetidine, ranitidine and famotidine.

4- **Proton-pump inhibitors:**

These are the drugs which inhibit proton (H^+) pump on gastric gland cells; by this inhibition the H^+ necessary for acid formation is not available decreasing acidity; e.g. omeprazole, pantoprazole and lanzoprazole.

DEMULCENTS

Def: These are drugs of high molecular weight which adhere to mucous membranes of gastrointestinal tract to protect it from inflammation. They form a colloidal solution (Thick) having an adhesive property and act mechanically.

Demulcents are grouped according to their source into:

1- Insoluble salts such as calcium carbonate, bismuth carbonate and aluminum silicate (Kaolin)
2- Sugars such as sucrose, lactose and related carbohydrates as honey and treacle (Molasses).
3- Gums such as gum acacia and gum tragacanth.
4- Gelatin and egg albumin.
5- Carbohydrates as starch, glycerin, paraffin and oils

Uses:

1- To relief inflammation of mucous membrane of gastrointestinal tract in cases of gingivitis, foot and mouth disease (ulcers of mouth), pharyngitis, gastritis, enteritis, etc. they are used in form of emulsion, suspension or enema.

2- To mask bad taste of drugs in mixtures.

EMETICS

Def: These are drugs which cause emesis (vomition) in vomiting animals.

- Man, dogs, cats and pigs can vomit as they have well developed vomiting center, while cattle and equine cannot vomit as they have no well developed vomiting center.

- There is chemoreceptor trigger zone (CRTZ) found on the surface of the medulla which convey nervous impulses to the vomiting center.

- Emetics are used in cases of recently ingested poisons or foreign substances still found in the stomach.

- CRTZ appears to carry dopaminergic receptors, therefore dopamine can induce vomiting and the response can be inhibited by dopaminergic antagonist.

Classification according to their mechanism of action:

1- Reflex emetics: The act by irritating sensory nerves of the gastric mucosa so reflex stimulate the vomiting center, they are given orally

acting after about 15 minutes till they reach to the pyloric end of the stomach where the sensory nerve are found.

Reflex emetics cannot cause vomiting in cases of poisoning with phenol or local anesthetics as they anaesthetize the sensory nerves of stomach, so no reflex impulse go to the vomiting center.

e.g. hypertonic solution of sodium chloride (5%) or copper sulphate solution 1%.

N.B. Sodium chloride hypertonic solution is more preferable than copper sulphate 1% solution as it is less toxic if absorbed.

2- Central (direct) emetics:

They act directly on CRTZ or vomiting center after their absorption. They act after about 5 minutes.

The best example of central emetic is "apomorphine HCL" which has a selective action on vomiting center.

It is usually given subcutaneously; emesis occur after 2-3 minutes.

If emesis doesn't occur by the first dose of apomorphine, do not repeat the dose as the centre may be depressed.

3- Mixed emetics: These are drugs which when given orally they irritate the gastric mucosa causing reflex vomiting and at the same time apart of it is absorbed in blood and directly stimulates the vomiting center such as ipecacuanha, digitalis, etc.

* In large doses, some other drugs when given by injection, they stimulate directly the vomiting center and a part is excreted in the

stomach. Through the bile which reflexly irritate gastric mucosa causing vomition such as antimony pot. tartarate (Tartar emetic).

ANT EMETICS

Def: these are drugs which can stop vomition. They are used in vomiting due to gastritis, travel sickness, during pregnancy.

1- **Local anti-emetics** are drugs act by protection of the gastric epithelium from irritation:

   a. **Anti-acids** which act by acid neutralization can reduce the symptoms of gastritis. Rapid acting compounds are those normally soluble in water, such as sodium bicarbonate. The slower anti-acids are the less soluble compounds such as calcium carbonate, mag. carbonate, aluminum silicate (kaolin).

   b. **Coaters** which coat and protect the gastric mucosa can inhibit gastric irritation such as calcium carbonate, bismuth carbonate and aluminum silicate.

   c. **Topical local anaesthetics** as benzocaine and amethocaine have been used to reduce vomiting in gastritis by depressing the sensory nerve endings in the stomach and so prevent the transmission of impulses to the vomiting center.

2- **Central anti-emetics** are drugs which act by blocking the dopaminergic receptors in the CTZ.

a. **Metoclopramide** is chemically similar to procainamide. It act on the CTZ and block the dopaminergic receptors so it inhibits vomiting. It is the most useful drug for both dogs and cats and is available for both oral and parenteral administrations.

b. **Phenothiazine derivatives** such as promazine and acepromazine, all have sedative, antihistaminic and antidopaminergic activities.

c. **Anticholinergic agents (parasympatholytics)** as atropine and hyoscine have some anti-emetic effect, and can be used in dogs to control motion sickness.

CARMINATIVES

Def: these are drugs given orally to facilitate expulsion of excess gases cumulated in the stomach, rumen or intestine by relaxing the sphinctors.

Uses:

1- Treatment of flatulent colic.

2- Tympany due to free gases.

In the normal process of gas, it is periodically removed by eructation.

* Tympany occurs when the eructation is inhibited, or the gas is unable to escape as in ruminal stasis.

Drugs used as carminatives are:

1- **Volatile oils** as peppermint oil, turpentine oil, camphor.

2- **Volatile anaesthetics** as chloroform water 0.04%, spirit of ether. They are given by mouth.

ANTIZYMOTICS

Def: These are drugs which decrease bacterial fermentation by killing or inhibiting rumen microflora, so decrease the production of gas. They may be given by stomach tube as a drench or injected directly into the rumen through a cannula.

- The use of volatile, turpentine oil remains as the only volatile oil used as an antizymotic.

- It is used to prevent excess production of gases in the rumen.

Tympany (free gases) can be treated by

1- Removal of already formed gases in the rumen either by
   a. Trochar and canula
   b. Carminative.
2- Giving ruminal tonics to activate ruminal motility as by carbachol, arecoline subcutaneously.
3- If gases still formed give antizymotics which are drugs prevent or lessens bacterial fermentation in the rumen as turpentine oil, phenol, antibiotics in small doses.

Frothy bloat (blocked gases) can be treated by:

1- Giving antifroth (antifoam) drugs which reduce the viscosity of ruminal fluids, so help blocked gases to be free as turpentine oil, organic silicones (methyl silicone).

2- Giving ruminal tonics and antizymotics. Frothy bloat may occur in animals grazing on pastures rich in plants contain high percent of saponins (as alfa alfa) which forms froth in the rumen causing bloat.

DRUGS AFFECTING INTESTINES

PURGATIVES AND LUBRICANTS

A purgative: is a drug which causes marked stimulation of intestinal motility and results in expulsion of intestinal content from the colon and rectum.

A lubricant: causes a similar action but the effect is milder and only help normal defecation without increase in the intestinal motility.

Uses of purgatives:

1- In chronic constipation, but not due to mechanical obstruction of the intestine.

2- In simple diarrhoea due to excess fermentation or due to presence of irritant poison in the intestine.

3- Given before or after anthelmintics to help expulsion of dead worms.

4- To remove a toxic material.

Classification: according to mechanism of action:

1- Lubricants (laxatives)

- They are only laxatives acting mechanically. They have oily nature.
- The best example of lubricants is "liquid paraffin"

- Liquid paraffin acts mechanically by forming an oily layer between the mucous membrane of the intestine and the hard stools. so help the descent of hard stools by lubrication.

- It has only laxative effect, helping normal defecation.

- It is used in chronic constipation in small animals.

2- Bulk purgatives:

The members of this group depend for their action on an increase in volume of the intestinal contents. This increase causes reflex contraction of intestinal musculature by stimulation of mechanoreceptors in the intestinal wall and an increase in power and speed of peristalsis.

a) Simple bulk purgatives

- They increase the bulk of non-absorbable contents of the intestine so reflexly stimulate intestinal peristalsis causing purgation.

- The best examples of simple bulk purgatives are:

Agre agar (sea weed), methyl cellulose (synthetic) and bran.

- They are inert powder (resistant to digestion in the gastrointestinal tract, which swell when taken with water so increase the intestinal content and reflexly stimulate defecation.

- They are used in chronic constipation for small animals.

- Bran can be used for large animals mixed with food.

- As a group, they are mainly of use in small animal particularly when sharp foreign bodies (needles, sharp bones) have been swallowed.

(b) Saline bulk (osmotic).

- These are alkaline salts as sod. sulphate and mag. sulphate.

- They are not readily absorbed from intestine so absorbe water from neighboring tissues and blood to neutralize osmosis, so increase water content and bulk of the intestine causing defecation of watery stools within 6 hours.

- They are given hypertonic solution.

- Saline purgatives are suitable for ruminants as purgatives, but not suitable for dogs as they cause gastric irritation.

- To enhance purgation, saline purgatives are given with a large amount of water.

- Mag. sulphate is better than sod. sulphate as it is not absorbed from intestine.

3- Irritant purgatives

They act by irritation of mucous membrane of the intestine.

a) **Direct irritant purgatives:** These include mainly caster oil, linseed oil and phenolphthaline.

Caster oil is hydrolyzed in intestine by bile into resinolic acid and glycerol. Resinolic acid will combine with sodium of bile forming sodium resinolate which exerts a mild irritant effect. The effect is seen

within 4-8 hours. A part of caster oil acts as a lubricant before hydrolysis. Caster oil is most suitable for dogs and cats and is better given in the form of emulsion.

Linseed oil acts is a similar way as caster oil except that the soap formed is sodium linolinate.

Phenolphthaline is a white powder and used as laboratory indicator. It possesses marked small and large intestine irritant properties. Phenolphthaline combines with sodium of bile forming sodium phenolphthalinate which irritates the intestinal mucosa causing purgation. A part of this salt is absorbed and excreted via the bile into the small intestine causing purgation. This cyclical action may continue for 2-3 days. The use of phenolphthaline is mainly limited to the pig, dog and cat. The main advantage of the drug is the prolonged period of action.

b) <u>Indirect irritant purgatives (Anthracene purgatives):</u> These are agents which require metabolism before irritations are produced. The main members of this group are the anthracene purgatives (aloes, senna, cascara, rhubarb) which contain mainly emodine and crysophanic acid. When the plants reaches the small intestine, the soluble active principles (emodine and crysophanic acid) are dissolved and absorbed then metabolized into irritant agents. The irritant substances are excreted into the large intestine, which is irritated and stimulated. Therefore, anthracene purgatives are of most value in animals of the large intestine like horses.

Because of this complex cycle, purgation is delayed for at least 18 hours after administration in the horse. The plants produce purgation accompanied with colicy pains, so antispasmodics as atropine are usually given with them. Moreover, they may induce abortion in pregnant animals. The powder of rhubarb contain a high proportion of tannic acid which act as intestinal astringent and induces constipation following purgation.

4- Neuromuscular purgatives (Hypodermic or Quick purgatives):

They act by stimulating the nerve supply of the intestine, so stimulating peristalsis causing purgation.

They act either by:

(a) **Stimulating parasympathetic** nerve e.g. acetylcholine, carbchol, arecoline.

(b) **Stimulating Aurbach's plexus** e.g. nux vomica, strychnine.

(c) **Direct stimulation to S.M.F.** e.g. Ba Cl_2

- Neuromuscular purgatives are given by subcutaneous injection acting after about 5 minutes.

INTESTINAL ANTISPASMODICS (SPASMOLYTICS)

Def: These are drugs which relieve spasms by relaxing the muscles of gastrointestinal tract. They are used in spasmodic colic in all animals;

they also reduce the rate of passage of intestinal content inducing a constipating effect.

Mechanism of action:

1- Parasympatholytics: atropine and hyoscine are commonly used for treatment of spasmodic colic and diarrhoea. They induce spasmolytic effect by blocking the muscurinic receptors of the intestinal muscle.

2- Direct intestinal muscle relaxants: some drugs have a direct relaxant effect on the intestinal muscle, e.g. papaverine, ether, chloroform and chloralhydrate and barbiturates.

3- Inhibiting aurbach's plexus as by morphine.

GASTRONINTESTINAL PROTECTIVES

Def: these are drugs which form a protective layer on the inflammed mucous membrane of stomach and intestine. They are used to treat gastritis, enteritis in cases of vomition and diarrhoea mainly in small animals.

- They are inert, inorganic non-absorbable fine powders.

- They act mechanically, the best examples are bismuth salts, ca. carbonate, aluminum silicate.

Insoluble bismuth slats.

As bis. carbonate, bis. oxide, bis. nitrate, bis. salicylate. They are used in gastritis and enteritis given orally usually combined with

ca. carbonate in cases of vomition and diarrhoea due to inflammation of gastrointestinal mucosa.

* Bis. carbonate is also impermeable to rays so used for radiological examination of gastrointestinal tract for tumors and ulcers.

Ca. carbonate and aluminium silicate (kaolin)

They act as protectives usually given with bis. carbonate in gastritis and enteritis in small animals.

INTESTINAL ASTRINGENTS

Def: These are drugs which check excess intestinal mucous secretion in cases of mucodial diarrhea due to enteritis and dysentery. (These compounds which precipitates protein of the intestinal mucosa to provide a protective barrier for the underlying tissue. Therefore, they act as a barrier between tissue and irritant substances. (This is useful for treatment of diarrhoea).

Types:

1- Vegetable astringents:

Tannic acid and plants containing tannic acid as catechu, krameria and kino are commonly used. The astringent action of tannic acid is rapid in onset as its conversion into inactive gallic acid is rapid.

Catechu, krameria and kino are preferred due to their lesser solubility and slow release of tannic acid. They are used in the form powder or tincture.

2- Metallic astringents:

Both aluminum and zinc salts have astringent action but their use is limited to external surfaces.

ADSORBENTS

Def: These are insoluble agents which can adhere other materials to their surface without chemical reaction.

- They adsorb toxins, poisons and small amounts of gases.
- They are used in cases of poisoning and simple flatulence in all animals.
- They are non-absorbable powders as charcoal, bis. carbonate and aluminum silicate.

DIGESTANTS

Def: These are drugs which help digestion of food, they are used in man and small animals as replacement therapy in cases of indigestion due to deficiency of certain digestive enzymes or secretions.

Digestants commonly used in medicine are hydrochloric acid, pepsin, pancreatic, bile salts, cellulose.

Diastase and takadiastase are vegetable ferment which are used to help digestion of carbohydrates.

DRUGS AFFECTING THE LIVER

The liver secretes bile to help digestion of fats and oils and help absorption of certain drugs. The gall bladder stores the bile. Bile descends to duodenum from the gall bladder through the bile duct and sphincter of Oddi by the contraction of the gall bladder.

CHOLAGOGUES

Def: These are drugs which help the descend of bile stored in the gall bladder into the intestine. They do not increase formation of bile. They are used in constipation and indigestion due to less bile in the intestine. They act either by:

- constricting the muscle of the gall bladder as by oily substances which help secretion of cholicystokinin hormone in the duodenum which contracts the gall bladder. Calomel also acts as cholagogue by reflex action from the stimulation of the intestine.
- Relaxing the sphincter of Oddi as by magnesium sulphate.

CHOLERETICS

These are drugs which stimulate liver cells to secrete more bile such as bile salts, dihydrocholic acid, oxgall extract, etc. Some drugs protect liver cells and prevent their destruction and help their regeneration such as choline, inositol (members of Vit. B complex), salbutol, lactualose (sugars) and bolds (plant), etc

Choleretics are used in cases of:

1- Indigestion due to less bile secretion.

2- Chronic liver diseases and cirrhosis.

3- To help absorption of Vit. K to form prothrombin.

VII. DRUGS ACTING ON THE RESPIRATORY SYSTEM

- **Physiological background**
- **Respiratory stimulants**
- **Expectorants**
- **Mucolytics**
- **Antitussives**
- **Bronchodilators**
- **Membrane shrinking drugs.**

BY: ABUBAKR M. EL-MAHMOUDY, PhD

PHYSIOLOGICAL BACKGROUND

- Respiratory rate is controlled by two mechanisms:
  - Nervous mechanism: The activity of respiratory center is modulated by impulses from the cerebral cortex, hypothalamus, lungs or circulatory system.
  - Chemical mechanism: CO_2 tension, O_2 level and pH of the blood affect the respiration. It is stimulated by CO_2 and acidosis.
- The main function of respiration is gas exchange, i.e. continuous supply of oxygen and continuous removal of CO_2 and other wastes. The lack of oxygen is called hypoxia or anoxia which is a diseased condition characterized by cyanosis and increase in respiratory rate to get as much oxygen as possible. There are 4 types of hypoxia according to its cause:
  - Anoxic hypoxia: due to inadequate availability of oxygen.

- Anemic hypoxia: due to decreased capacity of the blood to carry O_2 because of lack of hemoglobin or its change to nonfunctional one.
- Stagnant hypoxia: due to circulatory failure and stagnation of blood in its vessels.
- Histotoxic hypoxia: due to inability of tissue to utilize O_2 in spite of its presence due to cellular oxidative poisons as cyanide.

- Hypoxia can be treated according to the cause together with respiratory stimulants.
- Bronchial muscles are controlled by autonomic nervous system. They are contracted by parasympathetic stimulation (M receptors) and relaxed by sympathetic stimulation (β_2 receptors). Bronchoconstrictors are of no therapeutic value; on the other hand bronchodilators are very important drugs for asthmatic patients and during respiratory infection.
- The bronchial gland secretions are one of the defense barriers in the body. During infection the viscosity of the bronchial secretion may increase rendering it difficult for cilia to expel out. Such condition can be treated by mucolytics and expectorants.
- Non-productive cough due to continuous irritation of sensory nerve endings in the pharyngeal and laryngeal mucosae can be treated by antitussives.
- Respiratory infection is usually associated with inflammed swollen bronchial mucosa which causes dyspnea. Such condition can be helped by membrane shrinking drugs.

RESPIRATORY STIMULANTS

Def.: are the drugs which increase the depth and rate of respiration.

Members:

Respiratory stimulants can be classified according to their mode of action into:

A. Direct stimulants of the respiratory center; including:
   a. Medullary stimulants as picrotoxin, leptazole and nikethamide
   b. Cerebral stimulants as caffeine, ephedrine, amphetamine, atropine and hyoscine.
   c. Some analgesic drugs as salicylates.
   d. Carbon dioxide supplied as Carbogen (carbon dioxide-oxygen mixture; in which CO_2 tension is 5~10%).

B. Reflex stimulants of respiratory center; including:
   a. Stimulants of chemoreceptors in the carotid body and aortic arch by high CO_2 and low O_2 and acidic pH.
   b. Irritants to skin and mucous membranes by ammonia inhalation, aromatic spirit of ammonia oral administration, camphor or alcohol subcutaneous administration.

N.B. Some drugs act dually as you have studied in CNS.

Therapeutic uses of respiratory stimulants:

- During anesthesia.
- Coal tar poisoning.
- Conditions associated with hypoxia and bronchopneumonia.

RESPIRATORY DEPRESSANTS

Def.: are the drugs which decrease the rate and depth of respiration. They are of no therapeutic value.

Members:

Respiratory depressants can be classified according to mode of action into:

a. Depressants of respiratory center in the medulla as morphine and diamorphine.
b. Depressants of the sensitivity of respiratory center to CO_2 as barbiturates.

EXPECTORANTS

Def.: These are the drugs which:

- increase the volume of bronchial secretion,
- decrease its viscosity,
- and facilitate its expulsion by ciliary function and cough reflex.

Members:

Expectorants can be classified according to their route of administration into:

A. Inhaled expectorants

B. Ingested expectorants

A. Inhaled expectorants

- These are expectorant drugs given by inhalation either:
  - Directly in a confined air space
  - In steaming water
- They include:
  - Benzoin صبغة جاوا

- Eucalyptus oil
- Turpentine oil or its fraction "terebene"

Mode of action:

It is unknown but it is assumed that they may act directly on the bronchial gland cells.

- Application of inhaled expectorants is troublesome is animals but can be used in human practice.

B. Ingested expectorants

Def.: These are expectorant drugs given orally. They are subclassified into:

B.1. Reflex (nauseant) ingested expectorants

B.2. Direct (local) ingested expectorants

B.1. Reflex (nauseant) expectorants

Def.: These are emetic drugs but given by sub-emetic doses for expectoration.

Mode of action: They reflexly stimulate bronchial secretion via irritation of pharyngeal and gastric mucous membranes (a reflex involving parasympathetic pathway). The bronchial secretion is stimulated as prelude to vomiting.

Members:

- Ipecac (contains alkaloidal principles emetine and cephaline).
- Senega (contains the glycoside principle senegin).
- Squil (contains the glycosidal principle scillarin).
- Balsam of tolu (contains resin and benzyl benzoate)

- Ammonium chloride and ammonium carbonate: ammonium ions irritate gastric mucosa and reflexly stimulates bronchial secretion.

N.B. They are of no value in animals that can not vomit.

B.2. Direct (local) expectorants

Def.: these are drugs given orally, absorbed from the gut, producing its action elsewhere inside the body and then excreted via bronchial secretion.

Mode of action and members:

These locally acting drugs produce their effect during their pass through bronchial gland cells by either:

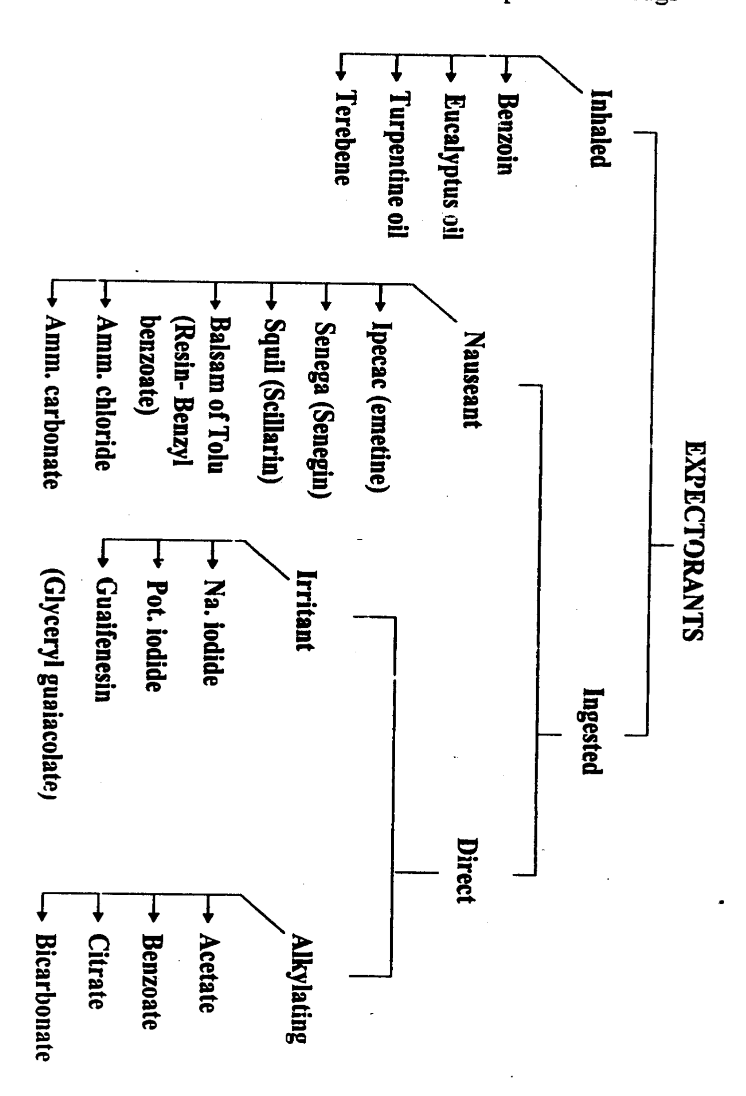
- Irritating them as Na. iodide, Pot. Iodide, Guaifenesin (glyceryl guaiacolate)
- Changing the acidic pH of infected secretion (which increases its viscosity) into alkaline pH (which decreases the high viscosity of the secretion) as acetate, benzoate, citrate and carbonate salts.

N.B. irritant expectorants are contraindicated in acute infection to avoid further paining.

Therapeutic uses of all expectorants:

- Productive or moist cough.
- Chronic and acute (but not irritant expectorants) bronchitis.

Fig. 35: Schematic classification of expectorant drugs



MUCOLYTICS

Def.: These are the drugs which liquefy the tenacious bronchial secretion and thus render them easier to be expelled by ciliary action, cough or expectorants. They are not considered as expectorants as they do not increase bronchial secretion.

Members and their modes of action:

1- Na. acetyl cysteine (Airbron)®	**2- Bromhexine (Bisolvon)®**
Given by inhalation	Given orally or parnterally
It produces relatively rapid liquefaction of tenacious mucoid and mucopurulent secretion reducing its viscosity.	It produces relatively slower liquefaction of tenacious mucoid and mucopurulent secretion reducing its viscosity.
Mode of action: it has –SH group in its structure and thus is able to break down the disulphide bridges between the glycoproteins of bronchial secretion with the result of reduction of viscosity of secretion.	Mode of action: it improves the lysosomal function and then lysosomal enzymes that hydrolyze the mucopolysaccharide polymers of the mucous.
3- Carboxymethyl cysteine (Mucolase)® - As Na. acetylcysteine but given orally - It can reduce bronchial gland hyperplasia that associates chronic bronchitis.	**4- Ambroxol (Mucopect)®** - It is the metabolite of bromhexine and thus similar to it. - Recent mucolytics contain ambroxol rather than bromhexine.

Therapeutic uses of mucolytics:

- Bronchitis and bronchiolitis associated with tenacious mucous.
- Removal of mucus plugs from small bronchiolar ramifications.
- Atelectasis and bronchioctasis caused by mucous plugs.

ANTITUSSIVES

Def.: These are the drugs which decrease the frequency of distressing cough.

Mode of action:

They interfere with the cough reflex either:

- peripherally at the level of pharyngeal and laryngeal sensory nerve endings,
- or centrally at the level of cough center in the medulla.

Members:

According to the previous modes of action, antitussives are classified into:

A. Peripheral or local antitussives
B. Central antitussives

A. Peripheral or local antitussives

Def.: these are the drugs which suppress the irritated sensory nerve endings in the pharynx, larynx and upper respiratory tract.

Members:

- **Demulcents:** as syrups, honey and oils.
- **Local anesthetics:** can be used in case of severe cough which may lead to lung damage or interstitial emphysema if not controlled.
- **Benzonatate (Tessalone)®:** a drug chemically related to the local anesthetic tetracaine.

B. Central antitussives

<u>Def.:</u> These are the drugs which suppress cough center directly in the medulla.

<u>Members:</u>

They are classified according to <u>their nature</u> into:

B.1. Non-opioid antitussives as oxeladine (Paxeladine)®

B.2. Opioid antitussives which are further classified into:

<u>B.2.1. Narcotic antitussives</u>, including:

B.2.1.1: Morphine, heroin, Methadone: they have antitussives action but their use is limited due to their addictive and respiratory depressant properties.

B.2.1.2: Codeine, dihydrocodeinone, pholcodine: they are very useful antitussives with the following advantages over morphine group:

- less addictive.
- less CNS depressant
- less respiratory depressant
- longer duration because of the relatively slower metabolism.

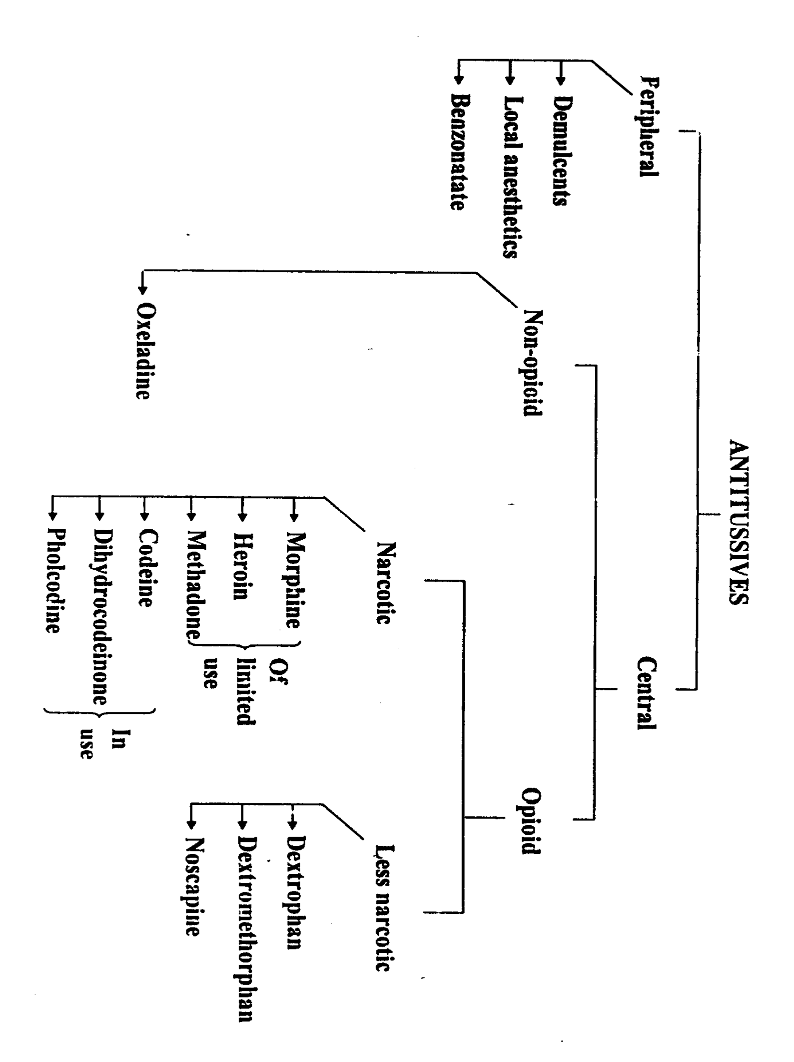
<u>B.2.2. Less narcotic antitussives</u>, including:

Dextrophan, dextromethorphan, and noscapine: They have minor sedative and narcotic properties with good antitussive effects.

<u>Therapeutic uses of antitussives:</u>

Non-productive (dry) cough.

Fig. 36: Schematic classification of antitussive drugs



BRONCHODILATORS

Def.: these are the drugs which produce relaxation of bronchial smooth muscle and thus widen the airway diameter.

Members:

Bronchodilators can be classified according to their mode of action into:

A. Parasympatholytics:

- As atropine and eucatropine via blocking of bronchial M receptors. These drugs have the disadvantage of drying bronchial secretion.
- Ipratropium (Atrovent)® is atropine derivative with no effect on bronchial secretion, therefore better as bronchiodilator.

B. Sympathomimetics, including:

B.1. Adrenaline and ephedrine which are mixed α- and β-receptor agonists. They have the side effects of hypertension (α effect) and tachycardia (β_1 effect).

B.2. Isoprenaline and orciprenaline which are mixed β-receptor agonists with tachycardia as side effect.

Both B.1. and B.2. are rapidly metabolized and thus used as aerosols. They are not convenient in animals.

B.3. Salbutamol, hexoprenaline, terbutaline and clenbuterol: they have the following advantages:

- Specific β2 agonists with less side effects.
- slowly metabolized and thus of longer duration.
- They can be given as aerosols and orally.
- Clenbuterol, particularly, is used very successfully in horses with many advantages including:
  - Effective in very small dose,

- Expectorant, in addition,
- Improves ciliary action.

C. **Direct relaxants**, including:

- Methylxanthines and their derivatives: Among xanthine alkaloids, theophylline, in particular, has a dominant smooth muscle relaxant effect. Derivatives of theophyllines with better kinetics have been developed such as: Aminophylline, diprophylline, and etamiphylline.
- As CNS stimulants, xanthines may also have the advantage of stimulation of respiration which corrects respiratory depression that may associate bronchoconstriction.

Therapeutic uses of bronchodilators:

- Bronchial asthma

MEMBRANE SHRINKING DRUGS

Def.: These are the drugs which normalize the inflammed swollen mucous membranes.

Members:

They are classified according to their nature into:

A. Decongestants:

- These are the drugs that relieve congestion by their vasoconstrictor action, including α_1-receptor agonists as noradrenaline, phenylephrine (Neo-synephrine)®, oxymetazoline (Afrin)® and xylometazoline (Otrivin)®.

B. Corticosteroids:

- As glucocorticoids and prednisolone.

- They produce decongestion and mast cell membrane stabilization preventing release of histamine which is vasodilator and bronchoconstrictor.
- They block uptake-2 of catecholamine and thus prolong their half life producing decongestion and bronchodilatation.

C. Antihistaminics:

- Some antihistaminics has parasympatholytic, local anesthetic, and CNS depressant actions which are beneficial for respiratory tract affections e.g. diphenhydramine.

Therapeutic uses of membrane shrinking drugs:

- Rhinitis.
- Nasal stuffness.
- Epistaxis.
- Bronchial asthma.

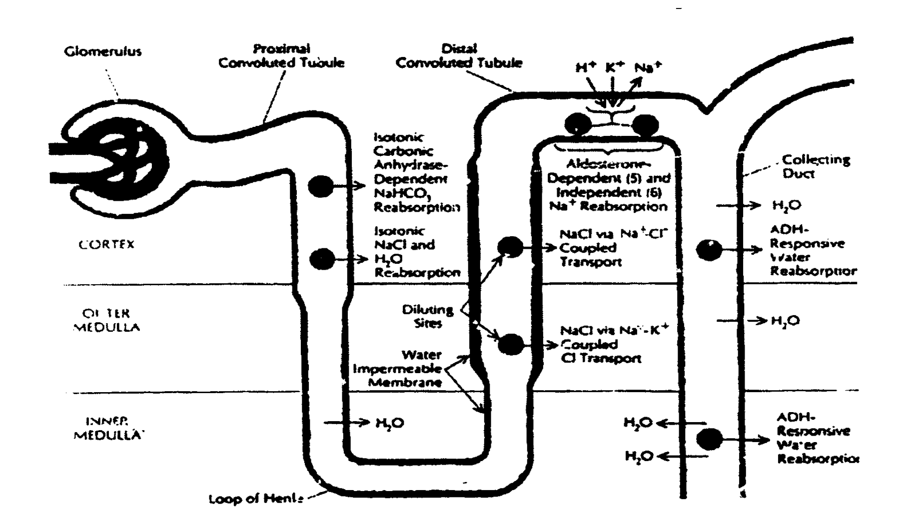
VIII. DRUGS ACTING ON THE URINARY SYSTEM

- **Background**
- **Diuretics**
- **Antidiuretics**
- **Uricosurics**
- **Renal blocking agents**
- **Urinary sedatives**
- **Urinary antiseptics**

BY: HOWAIDA M. EL-KHOLY, PhD

I. BACKGROUND

Fig. 37 Processes of salt and water transport in a nephron



The kidney regulates fluid and electrolyte balance by filtration, secretion and reabsorption

1. The kidney is an endocrine organ – it activates both erythropoeitin (for production of red blood cells) and vitamin-D (which regulates calcium metabolism). It also produces renin which affects various aspects of water and electrolyte homeostasis through its role in the renin-angiotensin-aldosterone system.
2. Urine formation and its volume and composition is determined by three processes:
   a. Glumerular filtration, about 125 ml of the plasma is filtered per minute through the Bowman's capsule. This filtrate is identical to the plasma without the protein.
   b. Tubular reabsorption or transport of materials from the tubular lumen to the circulation. In the proximal convoluted tubules, 80 % of the filtrate is reabsorbed. Water is reabsorbed passively with Na.
   c. Tubular secretion or transport of some materials from the blood to the tubular lumen. Some ions are secreted in the either in or in both of the proximal and distal convoluted tubules. The secretion of ions occur in response to the control of the pH of the plasma (H ions) and the concentration of certain waste ions (ammonia ions).

3. Body fluid and electrolyte composition are regulated by the kidney so drugs that interfere with renal transport may be useful in management of clinical disorders.
4. Diuretics are drugs which block renal ionic transport, causing diuresis (increasing urine volume), often associated with increase in sodium excretion.
5. Diuretics often act at different sites of the tubule transport system, at specific membrane transport proteins.

II. DIURETICS

Diuretics are the substances that increase the urine formation. They are classified according to their chemical structure and mode of action into:

1. Thiazides (Benzothiadiazines).
2. High ceiling (loop) diuretics.
3. Potassium sparing diuretics.
4. Osmotic diuretics.
5. Carbonic unhydrase inhibitors.
6. Acidifying diuretics.
7. Methylxanthines.
8. Mercurial diuretics.

Diuretics are also classified according to the site of action into:

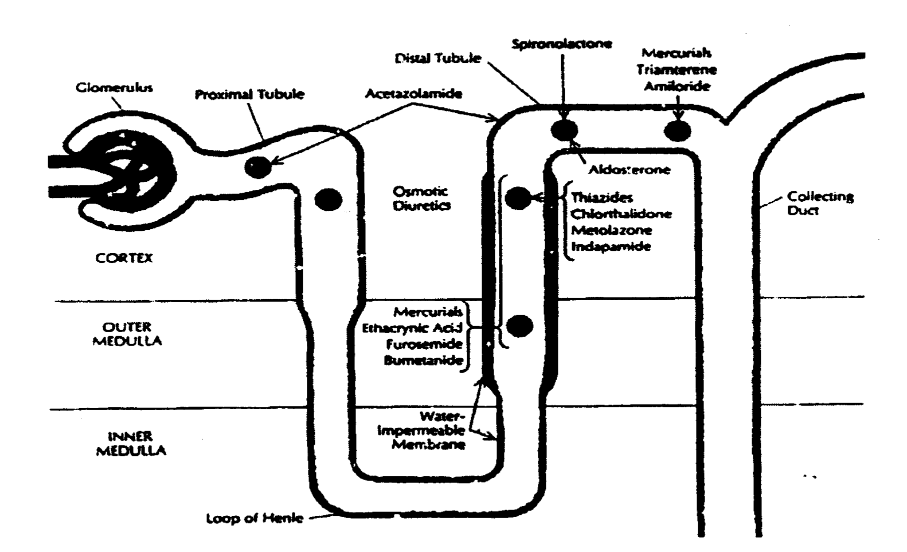
a. On the proximal convoluted tubules:
including carbonic unhydrase and osmotic diuretics.

b. On the thick part of the ascending limb of loop of henle:
including loop diuretics, mercurial diuretics and thiazides.

c. On the distal convoluted tubules:
including spironolactone, amiloride and triamctren

NB: it was noticed that some carbonic unhydrase inhibitors like acetazolamide work on the distal convoluted tubules also and thiazides work mainly on the early part of the distal convoluted tubules

Fig. 38 Site of action of diuretics



1. BENZOTHIADIAZINES (THIAZIDE DIURETICS)

The chief one of this group is **hydrochlorothiazide.**

Pharmacology:

Kidney: the diuretic effect occurs in the ascending limb of loop of henle and in the first part of the distal convoluted tubules. They produce their diuretic action by:

a. inhibiting the tubular reabsorption of sodium and chloride and the water passively accompanies the salt to the lumen.

b. inhibition of the enzyme carbonic unhydrase (acetazolamide-like action)

c. besides the inhibition of sodium and chloride reabsorption, they inhibit the secretion of calcium and increase the secretion of potassium and magnesium.

Antidiuretic effect: in case of diabetes insipidus due to nephrogenic cause that does not respond to antidiuretic (ADH) hormone.

Hypotensive effect: in case of hypertension, thiazides decrease the blood volume leading to decreasing the blood pressure.

Hyperurecaemic action: due to decrease in the uric acid excretion.

Therapeutic Uses:

- Management of edema in case of congestive heart failure, nephritic syndrome and liver cirrhosis.
- Hypertension
- Pregnancy toxemia
- Nephrogenic diabetes insipidus
- Calcium urolith

Precautions: caution should be taken when using thiazides in case of:

a. Renal insufficiency due decreasing the plasma volume,

b. Arrhythmias and using digitalis as thiazides will rise the plasma potassium level that evokes the digitals toxicity,

c. gout, **d.** diabetes mellitus, **e.** therapy with adrenocorticosteroids due to shooting up the level of blood plasma level.

Toxicity:

Overdosage of thiazides may lead to hypokalemia that precipitate digitalis toxicity (could be avoided by using small doses of KCl), renal or hepatic failure if taken in case of renal or hepatic insufficiency, rising in the uric and lipid in the plasma, diabetes mellitus in the pre-disposing individuals, dermatitis (thiazides have sulphonamide nucleus) and finally GIT troubles (nausea, anorexia, epiglotic pain, vomiting and diarrhea.

2. HIGH CEILING DIURETICS (LOOP DIURETICS)

They are the most potent kinds and are characterized they have rapid onset and short duration of action. They include frusemide, ethacrynic acid and bumetanide.

Action and mode of action:

Diuresis by inhibiting the reabsorption of sodium and chloride in the ascending limb of loop of henle Inhibition of NaCl reabsorption is followed by hypokalemia as the high concentration of NaCl in the distal tubules attracts out potassium ions. They tend to increase calcium and magnesium secretion and retention of uric acid in the blood and rising up the blood sugar level.

Therapeutic uses:

- Acute pulmonary edema - hypertension crisis - liver cirrhosis - severe congestive heart failure and in case of acute renal failure loop diuretics may increase the urine flow.

Side effects:

- Hypokalemia - hyperurecaemia -hyperglycemia
- GIT disturbance - increase the chance of ototoxicity in individuals taking gentamycin - allergic intertstitial nephritis and finally cross sensitivity with sulphonamides.

3. POTASSIUM SPARING (RETAINING) DIURETICS

A. **Spironolactone** is a competitive inhibitor of the natural mineralocorticoid hormone (aldosterone) and combines with its cytoplasmic receptor and prevents its action on Na^+/K^+ exchange in the distal tubules and results in increase in sodium and chloride loss and decreased potassium secretion.
The onset of action of it takes 2-3 days after administration. It is well absorbed in the GIT and metabolized in the liver.

Spironolactone is a **weak diuretic** that is used in case of **refractory edema** and is given with other diuretics like thiazides just to decrease **potassium loss**. Side effects include drowsiness, lethargy, headache, GIT disturbances and irregular menses.

B. Triametrene and C. Amiloride:

have the same action as they prevent the reabsorption of sodium and chloride and prevent potassium secretion in the distal tubules (at the

non aldosterone dependant area). Triametrine and amiloride are weak diuretics that are used in conjunction with another one to prevent potassium loss. They are different from spironolacton in that they are not aldosteron antagonists.

4. OSMOTIC DIURETICS

These are pharmacologically inert substances that are filtered freely in the kidney and their reabsorption is null. This group includes mannitol, urea and glucose. Mannitol is used in case of prophylaxis for acute renal failure, to lower the intra-occular and intra-cranial pressure and accelerate the renal excretion of some drugs like barbiturates and salicylates.

5. CARBONIC ANHYDRASE INHIBITORS

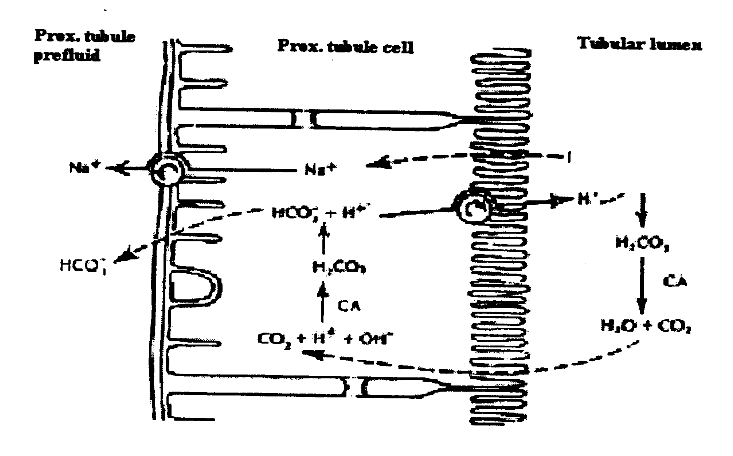
(acetazolamide, methazolamide, and dichlorphenamide)

They inhibit the carbonic anhydrase enzyme that is needed for the formation of carbonic acid from CO_2 and water and vice versa in the tubular cells and lumen (fig. 3).

Acetazolamide: By inhibiting the enzyme the H^+ ions will not be available for exchange with Na^+ that leads to high carbonate in the urine and acidosis due retention of hydrogen ions in the blood. As the tubular hydrogen is insufficient the tubular cells try to secret more potassium in an attempt to exchange it with sodium. At the mean while the urinary ammonia level drops as the hydrogen ion is not available in

the tubules for changing the ammonium ion into ammonia (NH_3 to NH_4). Acetazolamide is used in cases of glaucoma, mild intracranial hypertension, prophylaxis in altitude sickness, alkalinization of the urine in cases of cysteinuria and some condition of epilepsy.

Fig. 39: Carbonate cycle in the kidney



6. ACIDIFYING DIURETICS

This group includes ammonium chloride as it converts into urea in the liver and the excretion of urea increase the osmosis of the urine that cause diuresis. Using ammonium chloride for diuresis results in hyperchloremic acidosis so some chloride ions try to escape in the urine and results in forming ammonium chloride in the tubules and excreted in the urine. Once the excreted amount equals the

administered amount. no effect of it as diuretic. It is used in cases of glaucoma.

7. XANTHINES

This group includes theophylline, in the tea, (the most potent as diuretics) prescribed as aminophylline followed by theobromine, in the cocoa, is less potent but it has a long duration of action. The least diuretic effect in this group is the caffeine.

The mode of action as diuretics is by increasing the renal blood flow by increasing the cardiac output and vasodilatation of the afferent arteries and as a renal irritant that inhibits the reabscrption of sodium and chloride in the renal tubules.

Therapeutic uses: seldom used as diuretics due tolerance, gastric irritation and CNS stimulation.

III. AQUARETICS (ANTIDIURETICS)

Is the group that decreases the urine formation it includes:

1. ADH (vasopressin) that stimulates the V receptors in the collecting tubules. Stimulation of V receptors in the collecting tubules leads to insertion of additional water channel so it becomes more permeable for water collection and more concentration of urine.

It also increase the permeability of the collecting tubules for urea reabsorption that decreases the osmotic pressure of the urine that help the water channels for reuptaking water from the lumen to the precellular fluid.

ADH is also called **vasopressin** that constricts the blood vessel that is besides the water retention leads to rising up the blood pressure in case of hypotension and hypovolumia.

ADH antagonists are used in case of water intoxication due to inappropriate secretion of ADH, this group includes the antibiotic demeclocycline.

2. **Drugs** that constrict the renal afferent artery: morphine, nicotine, yohimbine, ether and cyclopropane.

3. **Thiazides:** they have antidiuretic action in case of diabetes insipidus of nephrogenic origin.

4. **Cyclopropamide:** has antidiuretic effect in case of diabetes insipidus of pituitary origin.

IV. RENAL BLOCKING AGENTS

These are the agents that block the tubular transportation of some other drugs eg. Para-amino-hippuric acid that prevents the tubular excretion of penicillin that prolongs its action and probencid that decreases the reabsorption of uric acid in the renal tubules.

V. URICOSORIC DRUGS

Are the drugs that either increase the secretion of uric acid like probencid or decrease the synthesis of uric acid like allopurinal that inhibits the xanthine oxidase enzyme that is responsible for the synthesis purines, the precursor of uric acid.

VI. URINARY SEDATIVES

Drugs that relieve the irritation due to inflammation in the urinary tract. Sedation occurs either by removal of the cause by using antibiotics and antiseptics or using atropine that relax the smooth muscle in case of calculi.

VII. URINARY ANTISEPTICS

Are drugs used to kill the microorganisms infecting the urinary tract. These materiais should be excreted in their active form from the kidney.

- **Hexamine:** is a white crystalline powder used as a prophylactic medication to protect the urinary tract from bacteria and fungi. In the acidic urine it is hydrolyzed into ammonia and formaldehyde and the later has antiseptic action.
- **Mandelic acid:** a keto-acid used as a urinary antiseptic in nephritis, pyelitis and cystitis. It must be excreted in the urinary tract unchanged in order to have a bacteriostatic effect; therefore, a strongly acid urine must be maintained during its administration.
- **Nitrofurantoin:** is an antibiotic that is used in case of simple cystitis without systemic illness and not used in case of nephritis, pyelitis or kidney abcess because it has poor bioavailabilty and low blood level, lower than the minimum inhibitory concentration (MIC).
- Specific drugs for UTI include: **Trimethoprim-Sulfamethoxazole combination, amoxicillin-clavulanate**

(Augmentin) and **quinolones** like ofloxacin, ciprofloxacin, norfloxacin, levofloxacin, gatifloxacin and sparfloxacin.

IX. DRUGS ACTING ON THE REPRODUCTIVE SYSTEM

- **Gonadotrophins**
- **Sex hormones**
- **Drugs affecting uterus**
- **Cervical dilators**
- **Drugs affecting sexual desire**

BY: HOWAIDA M. EL-KHOLY, PhD

These are the hormones and other drugs that affect the function of the gonads and the reproductive canals. They include the following:

- gonadortropins
- sex hormones
- ecbolics and uterine relaxants
- cervical dialators
- aphrodisiacs and anti-aphrodisiacs

I. GONADOTROPINS

GONADOTROPHIC HORMONES: Hormones that stimulate gonadal functions such as gametogenesis and sex steroid hormone production in the ovaries and the testis the major of the gonadotropins are glycoproteins produced primarily by the adenohypophysis (anterior lobe of the pituitary) and the placenta (chorionic gonadtropines). In some species, pituitary prolactin and placental lactogen exert some luteotropic activities. They are follicle stimulating hormone (FSH) and luteinizing hormone (LH).

FSH In females, the FSH stimulates the growth of immature Graffian follicles to maturation. As the follicle grows it releases inhibin, which shuts off the FSH production and in males, FSH enhances the production of androgen-binding protein by the sertoli cells of the testes and is critical for spermatogenesis.

LH (also known as **lutropin**) is a hormone synthesized and secreted by gonadotropes in the anterior lobe of the pituitary gland. In concert with the follicle stimulating hormone, it is necessary for proper reproductive function. In the female, an acute rise of LH – the *LH surge* – triggers ovulation. In the male, where LH had is also called **Interstitial Cell Stimulating Hormone (ICSH)**, it stimulates Leydig cell production of testosterone

HUMAN CHORIONIC GONADOTROPINs, hCG (PROLAN): It is produced by placenta of pregnant women. It appears in the urine and thus provides the basis of pregnancy tests as Friedman's test. It is considered the main source of commercial LH. hCG is extensively used as a parenteral fertility medication in lieu of luteinizing hormone. In the presence of one or more mature ovarian follicles, ovulation can be triggered by the administration of hCG. As ovulation will happen about 40-45 hours after the injection of hCG, procedures can be scheduled to take advantage of this time sequence. Thus, patients who undergo IVF, typically receive hCG to trigger the ovulation process, but have their eggs retrieved at about 36 hours after injection, a few hours before the eggs actually would be released from the ovary. As

hCG supports the corpus luteum, administration of hCG is used in certain circumstances to enhance the production of progesterone. In the male, hCG injections are used to stimulate the Leydig cells to synthesize testosterone. The intratesticular testosterone is necessary for spermatogenesis from the Sertoli cells. Typical uses for hCG in men include hypogonadism and fertility treatment

PREGNANT MARE SERUM (PMS): It appears in the serum of pregnant mares during the time period between 45th and 90th days of pregnancy. It is the main source of commercial FSH. When given parentarally it causes allergic reaction and induces tolerance so it is not used widely.

GONADOTROPIN-RELEASING HORMONE (gnRH) is a peptide hormone responsible for the release of FSH and LH from the anterior pituitary. gnRH is synthesized and released by the hypothalamus. gnRH is considered a neurohormone, a hormone produced in a specific neural cell and released at its neural terminal. A key area for production of gnRH is the preoptic area of the hypothalamus, that contains most of the gnRH secreting neurons. gnRH is secreted in the hypophysial portal bloodstream at the median eminence. The portal blood carries the gnRH to the pituitary gland, which contains the gonadotrope cells, where gnRH activates its own receptor, gonadotropin-releasing hormone receptor (gnRHR), located in the cell membrane then it is degraded by proteolysis within a few minutes. gnRH is available as gonadorelin hydrochloride for injectable use.

Studies have described it being used via an infusion pump system to induce ovulation in patients with hypothalamic hypogonadism.

Therapeutic uses of FSH:

- For induction of ovulation in non ovulatory females and for superovulation in case of invitro fertelization.
- For the treatment of hypogonadism in males.

Therapeutic uses of LH:

- In case of non ovulatory estrus cycle and nymphomania.
- In case of hypo-androgens in males.
- For correction of chryptorchidism.
- For late puberty.

Therapeutic uses of gnRH:

- Stimulation: Infertility due to hypothalamic hypogonadotropic hypogonadism (both sexes).
- Inhibition: management of prostate cancer, uterine fibroids, endometriosis, polycystic ovary syndrome, precocious puberty

II. SEX HORMONES

Sex hormones, also known as gonadal steroids, are steroid hormones which interact with vertebrate androgen or estrogen receptors. The term sex hormone nearly always is synonymous with sex steroid. Natural sex steroids are made by the gonads (ovaries or testes), by adrenal glands, or by conversion from other sex steroids in other tissues such as liver or fat. Sex steroids play important roles in inducing the body changes known as primary sex characteristics and

secondary sex characteristics. The development of both primary and secondary sexual characteristics is controlled by sex hormones after the initial fetal stage.

A. MALE SEX HORMONES: ANDROGEN is the generic term for any natural or synthetic compound, usually a steroid hormone, that stimulates or controls the development and maintenance of masculine characteristics in vertebrates by binding to androgen receptors. This includes the activity of the accessory male sex organs and development of male secondary sex characteristics. Androgens, which were first discovered in 1936, are also called **androgenic hormones** or **testoids**. Androgens are also the original anabolic steroids. They are also the precursor of all estrogens, the female sex hormones. The primary androgen is **testosterone**.

Therapeutic Uses of androgens:

- Impotency or decreased libido in males.
- Cryptorchidism
- Feminization
- Mammary tumors as in bitches.
- Estrus suppression in sexually active animals as dogs and cats.
- Aging and debility.
- Growth promotion for its anabolic activity.

B. FEMALE SEX HORMONES, ESTROGENS: are a group of steroid compounds, named for their importance in the estrous cycle, and functioning as the primary female sex hormone. Estrogens are

used as part of some oral contraceptives, in estrogen replacement therapy of postmenopausal women, and in hormone therapy for transsexual women. Like all steroid hormones, estrogens readily diffuse across the cell membrane; inside the cell, they interact with estrogen receptors. Estrogen is produced primarily by developing follicles in the ovaries, the corpus luteum, and the placenta. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) stimulate the production of estrogen in the ovaries. Some estrogens are also produced in smaller amounts by other tissues such as the liver, adrenal glands, and the breasts.

Therapeutic uses of estrogens

- Silent or absent heat
- Retained placenta and mummified foetus.
- Induction of abortion in the first days of pregnancy.
- Uterine inertia
- Contraception.
- Cancer of prostate.
- Growth promotion (increase fat deposition)
- Growth attenuation in jiant individuals

Estrogen antagonists: are used to treat estrogen-dependent breast cancer (like Tamoxiphen). Antagonists can also be used as fertility drugs (like Clomiphene) by blocking estrogen feedback to the anterior pituitary. This application of antagonists is effective because estrogen normally inhibits release of LH and FSH, permitting only a single egg to be released during each menstrual cycle and preventing overlapping

pregnancies. Females who overproduce estrogen do not ovulate due to this feedback, and estrogen antagonists can block the LH/FSH inhibition and get ova release. An obvious drawback of this treatment is the potential risk of increased incidence of multiple births.

PROGESTERONE

Progestins promote and maintain pregnancy. The natural progestin is progesterone. Progesterone is initially produced by the corpus luteum, which is the remainder of the ruptured ovarian follicle after it has released an egg (ova). If pregnancy occurs, the corpus luteum will continue to secrete progesterone for the first three months, after which the placenta becomes the supplier of both estrogen and progesterone. Progesterone prevents further ovulation during pregnancy by feedback to the hypothalamus with inhibition of LHRH (GnRH, FSH-RH). The main site of action of progestins is the uterus. After sensitization of the uterine endometrium by the estrogen, progesterone make the uterus thick and ready for the embryo implantation.

Therapeutic uses of progestagens:

- .Threatened or habitual abortion.
- Synchronization of estrus.
- Suppression of undesired estrus.
- Failure of implantation.
- In fattening of males by produce azospermia

III. DRUGS ACTING ON THE UTERUS

UTERINE STIMULANTS (ECBOLICS): Uterine stimulants are medications given to cause the uterus to contract, or to increase the frequency and intensity of the contractions. These drugs are used to induce (start) or augment (speed) labor; facilitate uterine contractions following a miscarriage; induce abortion; or reduce hemorrhage following birth or abortion.

1. Uterine stimulants are classified into:

- Direct like oxytocin, prostaglandins and ergot.
- Parasympathomimetics like acetyl choline and carbachole
- Indirect ecbolics like strong purgatives

The three uterotonics used most frequently (the direct ecbolics) are the **oxytocins, prostaglandins, and ergot alkaloids** that work directly on the uterus.

A. OXYTOCIN

Oxytocin is a naturally occurring hormone used to induce labor. The production and secretion of natural oxytocin is in the pituitary gland. It is also available in synthetic form under the trade names of Pitocin and Syntocinon. Oxytocine has a direct action on the myometium after sensitization with estrogen and the epithelial cells of the mammary gland that leads to let down of milk.

Therapeutic uses:

- Uterine inertia, when fetal position is normal and cervix is dilated.
- Retained placenta.

- Agalactia
- Postpartum hemorrhage and uterine bleeding.
- Uterine prolapse.

B. ERGOT ALKALOID:

It is an alkaloid obtained from ergot fungus (*Claviceps pupurea*). It could be also supplied as synthetic preparation "Methergin" which contains methylergometrine that is 10 times as powerful as ergometrine.

Actions and mode of action:

It specifically contracts uterine muscle directly with no or little effects on other muscles. Ergometrine has α-adrenergic blocking effect but methylergometrine has the advantage of lacking this effect. Both drugs stimulate the adrenergic system centrally.

Therapeutic Uses:

- Uterine inertia, when fetal position is normal and cervix is dilated.
- Retained placenta.
- Postpartum hemorrhage and uterine bleeding.
- Uterine prolapse.

C. PROSTAGLANDIN $F_2\alpha$:

- A **prostaglandin** is any member of a group of lipid compounds that are derived enzymatically from fatty acids arachidonic acid and have important functions in the animal body.

- Prostaglandins are synthesized in many tissues and act locally "local hormone".
- $PgF_2\alpha$ and PgE_2 are important for the body reproductive performances.
- $PgF_2\alpha$ could be also supplied as synthetic preparations "cloprosterol", "fluprosterol" and "prostalene" which have powerful luteolytic activities.

Actions and mode of action:

$PgF_2\alpha$ acts directly on uterine muscle cells causing contraction of the uteruine muscle which is more effective than oxytocin at earlier monthes. And play role in ovulation and luteolysis.

Therapeutic uses:

- induction of abortion.
- pyometra and mummified foetus.
- retention of placenta.
- synchronization of estrus.

2. UTERINE DEPRESSANTS

They are also called "uterine sedatives" or "uterine spasmolytics". These are the drugs which induce relaxation of myometrium maintaining pregnancy. They include the following groups:

- **CNS depressant** as perphenazine "major tranquilizer" and heroin "morphine derivative".
- **Adrenergic β_2 agonists** as clenbuterol. Mixed β_1 and β_2 agonists as "isoxuprine" could be also used. They have the side effect of stimulating the heart rate but have the

advantage of resistance to MAO and thus have long duration of action.

Therapeutic Uses:

- Threatened and habitual abortion.
- Uterine spasms.
- Overdosage of ecbolics.

IV. CERVICAL DILATORS

These are the drugs which relax the cervical muscle and dilate cervical ring. They are used at time of parturition when there is inadequate opening of cervix. They include:

Relaxin which is a dipeptide hormone formed by placenta, CL and uterus. At parturition, it relaxes pelvic ligaments and dissociates pubic symphesis.

Proquamezine which is a phenothiazine derivative with smooth muscle relaxant activity.

V. DRUGS ACTING ON THE SEXUAL DESIRE

1. APHRODISIACS

These are the drugs which increase sexual desire or libido. They are classified according to their nature into hormonal or non-hormonal aphrodisiacs.

A. Non-hormonal aphrodisiacs as:

- **Strychnine:** it stimulates sexual centers and spinal reflexes by inhibiting the spinal inhibitory transmitter glycine.

- **Yohimbine:** it has α-adrenergic blocking effect resulting in dilatation of cutaneous blood vessels especially those in genitalia causing erection. It also has CNS stimulant action.
- **Methyl alcohols:** they act as aphrodisiac by direct cutaneous vasodilatation resulting in erection; and by removal of social and sexual inhibitors by depressing CNS.
- **Cantharidin:** it acts as aphrodisiac during its excretion in urine where it causes irritation of pelvic area and increase in blood flow to sexual organs.

B. Hormonal aphrodisiacs as:

- androgen in males.
- estrogens in females.
- hCG in males and females.
- Thyroxine hormone which increases basal metabolic rate and thus improves sexual performance.

2. ANAPHRODISIACS

These are the drugs which suppress the sexual desire. It is used to normalize sexual hyperexcitability in males and females (nymphomania). They include:

- Sedatives as bromide
- Antiandrogens and estrogens in males.
- Antiestrogens, progesterone and LH in females.

X. DRUGS AFFECTING SKIN

- **Background**
- **Emollients**
- **Styptics**
- **Keratolytics**
- **Diaphoretics**
- **Counter irritants**
- **Depilatories**

BY: ABUBAKR M. EL-MAHMOUDY, PhD

BACKGROUND

The skin functions not simply as a passive barrier, but also as an important organ intimately connected to the immune and nervous systems. Many drugs are used for taking care of skin for protecting it or for treating bacterial, fungal and parasitic infections. Furthermore, transdermal drug delivery for systemic therapy is also applied.

Drugs used topically on the skin are either in the form of powder, or spray, or solution or lotion or ointments or creams or gels or plasters.

Most of drugs applied to the skin act locally, as the absorption from skin is slow. However, lipid soluble drugs are well absorbed when applied as such or incorporated in absorbable fatty bases as lanoline (sheep wool fat) or lard (hog omentum fat; hog is the caterated pig). On the other hand, drugs incorporated in nonabsorbable fatty bases as vaseline are not absorbed, yet these bases are still beneficial in protecting and hydrating skins in dermatological affections associated with dry fissured skin.

Agents and drugs acting on skin can be classified according to their nature of action into the following groups:

A. Skin sedatives
B. Skin stimulants
C. Other drugs

A. SKIN SEDATIVES

Def.: These are the drugs which sooth skin and reduce inflammation of the skin.

Members:

1. Emollients
2. Styptics
3. Diaphoretics
4. Local anesthetics
5. Demulcents
6. Astringents

A.1. Emollients

Def.: These are the drugs which soften and lubricate skin surface. They are also used as vehicles for some drugs.

Members:

Emollients are classified according to their source into the following groups:

Vegetable oils	Animal fats	Hydrocarbons
- Cotton seed oil	-Lanoline	-Liquid paraffin
- Caster oil	(Sheep wool fat)	-Vaseline
- Olive oil	-Lard	-Hard paraffin
- Almond oil	(Hog omentum fat)	

Therapeutic uses:

- Skin affections associated with dry fissured skin
- Skin protection
- Vehicles for some drugs.

A.2. Styptics

Def.: These are the drugs which stop superficial hemorrhage by precipitating epidermal and dermal proteins.

Members:

-Alum

-Tannic acid

- Ferric chloride 1%

A.3. Diaphoretics

Def.: These are the drugs which increase the amount of sweat.

Mode of actions and members:

- Drugs which stimulate heat regulating center as salicylates
- Drugs which stimulate sweat center in the spinal cord as camphor and ammonium citrate.
- Drugs which stimulate peripheral nerves of sweat glands as pilocarpine.
- Drugs which stimulate sweat gland cells during their execretion as volatile oils.

N.B.1 Diaphoretics are of no value in animals having no sweat glands such as dogs and cattle.

N.B.2 Other skin sedatives are studied in their respective sections.

B. SKIN STIMULANTS

Def.: These are the drugs which induce inflammation and increase the peripheral vascularity.

Members:

1. Keratolytics
2. Counter irritants

B.1. Keratolytics

Def.: Drugs which remove thickened skin, corns and warts.

Members:

- Salicylic acid (20 % in collodion)
- Benzoic acid (20% solution).
- Resorcinol (up to 10% solution)

B.2. Counter irritants

Def.: Drugs applied to the skin with friction to produce local irritation and acute inflammation. They are used for treatment of chronic inflammation in certain parts of the body especially ligaments, tendons and joints.

Acute inflammation increases the peripheral vascularity to the chronically affected area supplying good nutrition and removing waste products with final recovery of the affected area.

Mode of action:

Counter irritants act reflexly by stimulating sensory nerve endings of the skin.

Stages:

According to the severity of the used counter irritant, one of the following stages could be obtained:

1- Rubifacient: where application of the counter irritant drug produces only congestion and redness of the affected part. Rubifacient drugs are used as anodynes to remove pain in rheumatism.

2- Vesicants: where application of the counter irritant produces not only congestion, but also cumulation of serous fluid under the skin forming vesicles or blisters.

3- Pustulants: where application of the counter irritant produces severe inflammation converting vesicles to pustules containing tissue debris and inflammatory cells with suppuration; and sometimes all the skin layers are removed exposing the subcutis with ulceration.

<u>Members:</u>

A. Drugs which can be used as <u>rubifacients</u> include:

1- Hot water and massage

2- Kaolin cataplasma لبخة الكاولين.

3- Camphor as liniment

4- Turpentine oil as liniment

5- Methyl salicylate as liniment.

6- Iodine as tincture or ointment

7- Plasters as capsicum plaster لزقة قرن الشطة.

B. Drugs which can be used as vesicants or blisters include:

1- Green blister, which is made from cantharidis (dried powder of Spanish fly) that contains the irritant active principle cantharidin.

2- Red blister, which is made from bin-iodide of mercury (1:8)

3- Iodine strong tincture (5%) or iodine ointment (10%).

C. Drugs which can be used as pustulants include:

1. Croton oil.
2. Thermo- and electro-cautery.
3. Firing.

Therapeutic uses of counter irritants (all stages):

1. Chronic inflammation.
2. Rhumatism.
3. Lumbago and lower back pain.

C. OTHER DRUGS AFFECTING SKIN

These include other groups of drugs as depilatories مزيلات الشعر, antiseptics and cleansing agents المنظفات.

Depilatories are substances which remove hair from the skin.

Hair can be removed mechanically (by adhesive pastes) or chemically (by using some drugs as barium sulphide which dissolves the shaft of the hair fibers).

N.B. Antiseptics and cleansing agents will be discussed in their respective section.

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